THE EARLY DIAGNOSIS AND MANAGEMENT OF CREUTZFELDT-JAKOB DISEASE

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ABSTRACT

This thesis describes work undertaken to improve the early diagnosis of variant Creutzfeldt-Jakob disease (vCJD), using existing clinical and research tools. Twenty-one cases referred to the National Hospital for Neurology and Neurosurgery and St. Mary's Hospital, London with suspected vCJD completed participation in the study. Fifteen cases were confirmed with definite or probable vCJD and six were given alternative diagnoses. These six cases with alternative diagnoses formed a control group. Further controls were recruited from patients referred with sporadic and familial forms of prion disease.

A neuropsychiatry questionnaire comprising a battery of standardised tests was formulated. Of those with definite or probable vCJD, 86% exhibited anxiety, 93% irritability, 64% agitation and 79% displayed evidence of severe depressive symptoms. Fifty seven percent experienced simple delusions, most commonly of theft and suspicion and 36% described misidentifications (mean 8 months from illness onset). Behavioural change was common to all cases, 79% with aggression, 71% emotional lability and 79% sleep problems.

Comprehensive neuropsychology assessments from those with vCJD were compared with sporadic and familial cases. Moderate to severe intellectual decline is characteristic of vCJD and impairment affects all cognitive domains. Only a minority of the vCJD cases presented with perceptual impairment compared with 50% of sporadic and familial cases. The proportion of cases with nominal impairment in the familial disease group was significantly lower than in the variant and sporadic groups.

Serial volumetric MR imaging was only possible in a subgroup of cases with familial CJD. The annual mean rate of whole brain atrophy was 2.05% compared to 0.25% in normal controls. Single voxel proton magnetic spectroscopy performed in three cases with vCJD showed a 2.5 fold (150%) increase in the mean myo-inositol concentration and 50% reduction in N-acetylaspartate in the pulvinar region. Similar changes were seen in the caudate nucleus where no signal change was detected on T2 weighted images.

The key to early diagnosis still relies on a high index of suspicion for vCJD and early referral to the appropriate specialist services. First hand experience of the problems faced by patients prompted a second, parallel project to be undertaken. A survey was conducted of all UK consultant neurologists and old age psychiatrists to assess current practices in the diagnosis and management of young people with dementia. It was concluded that young people may be under investigated if managed solely by an old age psychiatrist and may not receive adequate follow up services if managed solely by a neurologist.

DEDICATION

This thesis is dedicated to my husband Roger and our daughters, Rachel and Justine. Roger has provided untiring support with patience and encouragement, always giving sound judgement and advice. Rachel and Justine have both been born since I started this work. Their happy, inquisitive natures and excitement for life are an amazing new source of inspiration.

"The way to love anything is to realize that it might be lost"

G.K. Chesterton (1874-1936).

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Characterisation of a new disease

The first cases of vCJD in humans were recognised in 1995[1-3]. The young age at onset of the original cases, the clinical phenotype and appearance of certain pathological characteristics distinguished these cases from other forms of CJD. These considerations, together with the knowledge from surveillance (re-instigated in 1991 following the BSE epidemic in cattle) of the rarity of sporadic CJD in people under the age of 40 years, led to the suggestion of a new disease appearing in humans. Our knowledge of these very rare diseases is rapidly evolving, drawing on aspects of protein biology, neurogenetics and epidemiology. This together with the experience of clinicians and pathologists involved in the study of sporadic, familial and acquired cases (including the study of Kuru in the Fore people of Papua New Guinea), is assisting the characterisation of this new disease.

CJD is often difficult to diagnose in the early stages due to its insidious onset, with prominent psychiatric features including personality and behavioural change. Certain psychiatric features appear to be characteristic including symptoms of depression, the occurrence of delusions and hallucinations, and the prominence of behavioural symptoms including problems with sleeping and aggressive behaviour[4]. Other early features include sensory changes, dysaesthesiae, gait disturbance and chorea or myoclonus[5]. Although there are characteristic features of vCJD, there are case reports in the literature of unusual presentations of the disease[6]. Cases have now been reported in childhood and the elderly and these need to be carefully documented to establish the clinical phenotypes in these different age groups[7]. Similarly, there needs

to be a high index of suspicion of cases with variations in the methionine/valine polymorphism at codon 129 of the prion gene that is linked to susceptibility to the disease. To date all cases of vCJD have been methionine homozygous at codon 129 of the prion gene. The appearance of CJD in population groups with other polymorphisms at this location (MV or VV) may be very different. It is vital that there is further detailed characterisation of the early clinical, psychiatric and cognitive aspects of this new and evolving disease.

The need for an early diagnosis

An early diagnosis is important in vCJD for several reasons. The burden of illness falling on the young patient and their family has profound implications on family life, employment prospects, family finances and life within the home. An early diagnosis may allow the patient to discuss the implications with their loved ones and to be involved in helping to make financial/legal arrangements. The illness is rapidly progressive, with the patient rapidly becoming fully dependent for all aspects of care. Being aware of the diagnosis allows the appropriate services and support to be in place early, predicting problems before they occur. With the emergence of possible disease modifying agents for prion diseases, there is new impetus to instigate therapy at the earliest opportunity.

It is very difficult to assess the risk of transmission of vCJD from a person with unsuspected, sub-clinical infection who undergoes surgery, donates blood or organs, or who visits the dentist, for example. Confirmation of the diagnosis allows appropriate infection control measures to be implemented to reduce the possible risk of further transmission of the disease.

Study outline I: Using psychiatric, cognitive and neuroimaging tools in the early diagnosis of vCJD

The aim of the work performed in this study was to assess the application of the available, reliable, non-invasive tools of psychiatry, neuropsychology and neuroimaging in the early diagnosis and further characterisation of, vCJD. It involved the prospective study of all patients referred to the National Hospital for Neurology and Neurosurgery and St. Mary's Hospital, London with a possible diagnosis of vCJD between May 1998 and May 2002. Serial clinical, psychiatric, cognitive and imaging studies were performed at baseline and over the subsequent months in all cases, irrespective of the final diagnosis. Results of investigations could therefore be compared between positive cases of vCJD and those with an alternative diagnosis. Results of investigations were also compared with a group of patients with a confirmed diagnosis of a prion disease, of the sporadic, familial or iatrogenic forms. Most cases referred with possible vCJD underwent tonsil biopsy. Pathological confirmation of the disease and correlation with clinical and imaging features was attempted.

Study outline II: National survey to assess current practices in the diagnosis and management of young people with dementia

Seeing at first hand the experience of patients and their families through the diagnostic process and the subsequent follow up, support and services offered to young people with dementia prompted a second, parallel project to be undertaken. There is often a delay in patients with young onset dementia being referred to

specialist services due to the insidious onset of these illnesses, including CJD. There are also concerns however that referral between specialists, particularly neurologists and old age psychiatrists is incomplete and that patients may be under-investigated or inappropriately followed. A survey was conducted of all consultant neurologists and old age psychiatrists in the UK, to assess current practices in the diagnosis and management of young people with dementia. It was designed to look at the current level of referral between specialists, how each investigates their patients and details of follow up care. The results are discussed in the light of the recommendations of both the task force set up by the European Federation of Neurological Societies (EFNS) to look at the management of patients with dementia and the guidelines of the American Association of Neurologists.

INTRODUCTION

The prion diseases

The prion diseases or transmissible spongiform encephalopathies (TSEs) are a group of rare neurodegenerative diseases affecting animals and humans. The earliest records, dating back to the 18th Century, describe Scrapie, a naturally occurring prion disease of sheep and goats, which is now endemic in many parts of the World. Other TSEs include chronic wasting disease (CWD), which is naturally occurring in native North American deer and wapiti[8]. It was first recognised by biologists in the 1960's as a disease syndrome of captive deer held in wildlife research facilities in Colorado, but was not recognised as a TSE until the 1970's[9]. The TSEs were dramatically brought to the attention of the wider scientific community and the public with the emergence of the epidemic of bovine spongiform encephalopathy (BSE) in the UK in 1986[10]. Coincident with this, spongiform encephalopathies have been described in a wide variety of captive cats and other zoo animals. Some of these have been shown to be caused by a BSE like prion strain[11&12] and is seems likely that the vast expansion in the host range of the spongiform encephalopathies is due to transmission of BSE from cattle to other species. Surveillance for the human prion diseases was re-instituted in 1991, when concerns were raised about the possibility of transmission to humans of BSE. The occurrence of five cases of apparently sporadic CJD in young people in the UK in 1995/1996 warranted further investigation, leading to the discovery of the new disease, vCJD[1-3].

The human prion diseases

The human prion diseases were first described by Creutzfeldt and Jakob, with the eponym being introduced by Spielmeyer in 1922[13]. The traditional classification of the prion diseases included, CJD, Gerstmann-Straussler-Scheinker syndrome (GSS) and Kuru, but very little was known about the cause of these diseases. It had been known since 1936 that scrapie could be transmitted via inoculation, between sheep and goats[14] but it was not until the recognition of Kuru in the 1950s and its similarities to scrapie, that transmission of first Kuru and then CJD and GSS to primates by intracerebral inoculation was attempted[15-17]. This led to the description of the transmissible dementias and new diagnostic criteria were created. Cases could be diagnosed on their transmissibility and the occurrence of common, classical histopathological features of spongiform change, neuronal loss and astrocytic proliferation.

The nature of the infectious agent

Over this time, there was much debate over the nature of the transmissible agent, which was assumed to be a "slow virus", although no systemic reaction or clinical markers of infection were seen and no virus was ever isolated. The agent did not behave as if it contained nuclei acid and it was suggested that it might simply be a protein[18&19]. Griffith, in 1967 proposed the protein-only hypothesis[20], suggesting that the infectious agent may be a modified form of a normal cellular protein. Prusiner purified the scrapie infectious agent in 1982[21]. This was termed the prion protein. The prion gene has subsequently been cloned, on chromosome 20.

Prion biology

The prion protein (PrP^c) is a normal, host encoded, glycosylphosphatidylinositol (GPI)-anchored glycoprotein. This is converted into an abnormal disease forming isoform, PrP^{Sc}, by a post-translational conformational change[22]. PrP^c contains about 40% alpha helix and very little beta pleated sheet, whereas PrPSc is composed of 30% alpha helix and 45% beta sheet. This conformational change is accompanied by marked changes in the physicochemical properties of the prion protein such that it becomes partially resistant to proteolytic degradation and insoluble in nondenaturing detergents[23]. There are several models for the propagation of PrP^{Sc}. One model, the "refolding model" suggests that PrP^{Sc} comes into contact with a normal PrP^c molecule and induces it to change shape and form more PrP^{Sc}[24]. This process leads to an exponential conversion cascade. The "seeding" model suggests that PrP^c and PrP^{Sc} are in equilibrium (heavily weighted to PrP^c). PrP^{Sc} is stabilized when it adds onto a seed or aggregate of PrP^{Sc}. The seed slowly grows and gradually more PrP^{Sc} aggregates swinging the equilibrium towards producing more PrP^{Sc} from PrP^c[25]. It is now generally believed that PrP is delicately balanced between the native alpha and beta forms with a high-energy barrier between them. The balance could be altered by a mutation in the gene producing an abnormal gene product in familial forms of the disease, by inoculation of a seed of beta PrP as in acquired forms or by a rare stoichastic conformational change leading to sporadic forms, thus accounting for all of the possible aetiologies of prion disease.

The role of PrP^c in the normal cell remains unclear. The gene is well conserved in mammalian species and there is greatest expression in the central nervous system and immune system[8]. It is thought that it may play a role in cell signalling or adhesion.

The N terminal of the molecule has a segment of five repeats of an eight amino acid sequence (known as the octarepeat section). This contains one of the binding sites for copper on the molecule. It may be that PrP^c has a role in copper transport and that a conformational change leads to disruption of this leading to neurotoxicity.

Prion strain diversity

There is species variation in the gene encoding the prion protein. On transmission of prions between or within species, PrP sequence is specified by the host (the recipient). The prion strain is enciphered in the conformation of the PrP^{Sc}, from the source. This interacts with recipient PrP^c to determine the tertiary structure of the host (recipient) PrP^{Sc}. The PrP^{Sc} molecular types were traditionally shown to be maintained on passage in transgenic mice with human PrP and they could be distinguished by their biological properties[12]. The diseases varied in their incubation periods and neuropathological features. It has been possible recently, to associate several human PrP^{Sc} molecular types with certain phenotypes of prion disease. For example, Hill and colleagues describe three PrP^{Sc} subtypes among cases of sporadic and iatrogenic CJD and a distinct type 4 pattern in vCJD[12&26]. Parchi et al describe two PrP^{Sc} molecular types in classical CJD[27]. Molecular strain typing has greatly refined the diagnosis of vCJD and may allow transmission to other species to be determined more easily.

The species barrier and susceptibility to prion disease

There is a species barrier to the transmission of prions such that on inoculation of prions from one species to another, not all of the animals will succumb and those that do will have longer and more variable incubation periods. A second passage to the recipient species resembles a within species transmission with most animals affected with the original, shorter incubation period. It is suggested that this is due to differences in the tertiary structure of PrP in different species (in turn affected by PrP^{Sc} conformation and primary amino acid sequence), which makes their direct interaction less efficient. Certainly there are a higher proportion of individuals homozygous for methionine or valine at codon 129 in those with sporadic and iatrogenic CJD, suggesting that an identical prion primary structure makes interaction more efficient[28]. A species-strain barrier may now be referred to, recognising that prion PrP^{Sc} molecular subtype affects transmission properties between species. Hill et al, 1997 showed that vCJD prions (human PrP) transmit to wild type mice more effectively than those in classical CJD but they transmit less efficiently to transgenic mice expressing only human PrP[26].

Classification of prion diseases

The prion diseases are now classified into sporadic, familial, and acquired forms. Sporadic CJD is the most common form and is found Worldwide with an incidence of one case per million per year. A mutation in the Prion gene is found in approximately 15% of cases of human prion disease. There are over 20 different mutations now recognised with great diversity of clinical and pathological features. Prion diseases can be acquired by iatrogenic means or from oral exposure through for example,

cannibalism (Kuru) or an infected food chain (BSE). It is assumed that BSE has been transmitted through the oral route but the exact source is not known.

Sporadic CJD

Classical, sporadic CJD is a rapidly progressive neurodegenerative disorder with multifocal dementia and often myoclonus. It has onset usually between 45 and 75 years of age, with peak onset at 60-65 years. Prodromal features of depression, malaise, insomnia, weight loss, headaches and other non-specific pains occur in about one third of cases. This is followed by progressive cognitive impairment, myoclonus, pyramidal, extrapyramidal, cerebellar signs and sometimes cortical blindness. Progression to akinetic mutism can occur within a matter of weeks and approximately 70% of cases die in less than six months. The pathological hallmarks of spongiform change, neuronal loss and reactive gliosis may vary greatly in their degree and distribution[8].

Recent analysis of molecular and clinicopathological features of a large series of sCJD patients identified six distinct clinicopathological groups, which could be distinguished by the codon 129 polymorphism (methionine or valine) and the prion strain type (MM1, MV1, VV1, MM2-C, MM2-T, MV2, VV2)[27]. The classical myoclonic or Heidenhain variants constituted about 70% of the series and were accounted for by the MM1 and MV1 groups. They were characterised by a rapidly progressive dementia with early myoclonus, and 40% of cases had visual impairment or unilateral signs at onset. This group usually have characteristic EEG features. The characteristic spongiform change, neuronal loss and gliosis were often prominent in the occipital cortex and PrP staining was of the "synaptic type". The VV2 group

included patients previously classified as the ataxic variant and accounted for 16% of the cases. They tended to have ataxia at the onset with dementia occurring late and no typical EEG features. This is supported by more prominent involvement pathologically of the subcortical/brain stem nuclei with spongiosis in the deeper layers of the neocortex. PrP staining tended to be in plaque like focal deposits. 9% of the cases were of the Kuru – plaque variant, or MV2 group. This group had a longer mean duration of symptoms (17.1 months) and cognitive impairment more commonly from the outset. There were usually no typical EEG features. The distinguishing feature of this group was the presence of amyloid-Kuru plaques particularly in the cerebellum. The other groups represent 5% of cases and were much rarer. The MM2 – thalamic group included those cases previously described as the thalamic form of CJD and Familial Fatal Insomnia (FFI). Insomnia and hyperactivity occurred in most cases with ataxia and cognitive impairment. There was characteristically prominent atrophy of the thalamus and inferior olive. Spongiosis may be focal or absent. The MM2 and VV1 groups show cortical signs and progressive dementia, without cerebellar signs or classical EEG features. These groups are distinguished by their pathological features. In the MM2 groups, there are usually large confluent vacuoles in all cortical layers.

Familial CJD

Hereditary prion disease is diagnosed by the presence of a mutation in the prion gene, leading to an autosomal dominant pattern of inheritance. There are over 20 known mutations, which are either point mutations or insertions encoding additional copies of the octapeptide repeat present at the N terminal end of the prion molecule. There is a wide spectrum of diseases with very varied clinical phenotypes and pathological

features. Classically, GSS presents in the third to fourth decade with chronic cerebellar ataxia and pyramidal signs, with dementia occurring late in the illness. There are multicentric PrP-amyloid plaques histologically[29]. These cases have been difficult to diagnose in the past as there may be great variability in the phenotype of the illness even within one family with the same mutation and some unusual cases may not have the characteristic pathological features of prion disease[30]. Some mutations, for example the 144 base pair insertion, characteristically have a prodrome of behavioural and personality problems from an early age. The illness duration is usually long compared to that of sporadic cases and common features include progressive cerebellar ataxia, chorea, myoclonus, pyramidal and extrapyramidal signs, dementia and rarely amyotrophic features[31].

Acquired forms of CJD

The iatrogenic transmission of Creutzfeldt-Jakob disease (CJD) was first recognised in 1974 in a recipient of a corneal graft from a donor who had died of undiagnosed CJD[32]. Transmission has subsequently been demonstrated following neurosurgery[33], stereotactic electroencephalography[34], dura-mater implants[35] and after the administration of human pituitary-derived growth hormone and gonadotrophin[36&37]. The incubation period and clinical phenotype of the ensuing illnesses vary with the route of inoculation. When infection is introduced directly into the central nervous system, the incubation period is short (months) and the disease resembles classical sporadic CJD with a progressive dementia syndrome. Inoculation via a peripheral route produces an illness with an incubation period of years (or decades) and a predominantly cerebellar onset[38&39].

Kuru is a prion disease discovered in a tribe living in the Eastern Highlands of Papua New Guinea in the 1950's. The Kuru epidemic is thought to have started from the random occurrence of a case of sporadic CJD in a tribe member, and spread by oral inoculation at the time of his or her death after ritualistic cannibalism. The disease affects males and females, but with a preponderance for women and children. The women and children were given the brain and internal organs at such feasts. The disease onset ranged from 5 years to over 60 years and incubation periods are estimated as lying between 4.5 years and over 40 years (mean 12 years). The disease has a distinctive clinical phenotype with a predominant cerebellar ataxia, and dementia occurring only late in the illness[8].

Bovine Spongiform Encephalopathy

Although some scientists believe that BSE may have first appeared in the 1970's, it was not until 1986 that it was formally described by Gerald Wells (neuropathologist at the Central Veterinary Laboratory (CVL))[10]. It was presumed that the infection could have resulted from the feeding of scrapie infected meat and bone meal (MBM) to cattle. It is now felt that the epidemic may have started from a novel source, such as rare sporadic cases of BSE in cows that entered the food chain[8]. The source of infection to humans i.e. the infectious material is still not defined, but it is known that sheep are susceptible to BSE and that there is a risk not only from bovine materials but also of transmission of BSE through sheep to humans (WHO Consultation on Public Health and Animal TSEs Epidemiology, Risk and Research Requirements, 2000)[9].

A ban was put on the use of specified bovine offal (SBO) in 1989 and in the same year, many restrictions were put on UK beef exports. In 1990, the government set up a new scientific advisory committee, the Spongiform Encephalopathy Advisory Committee (SEAC), to advise the Ministry of Agriculture, Food and Fisheries (MAFF) and the Department of Health (DOH). The CJD Surveillance Centre was set up in Edinburgh.

The emergence of variant CJD

In October, 1995 there were two cases reported in the Lancet of apparently sporadic CJD aged 16 and 18[1&2]. In April 1996 the CJD surveillance unit reported 10 young cases with certain clinical and pathological characteristics, which distinguished them from cases of sporadic CJD and it was considered likely that this was a new disease, termed new variant CJD[40]. By this time there had been over 30,000 suspected cases of BSE-infected cattle in the UK. Although the size of the epidemic of BSE in cattle has been by far the greatest in the UK, it is a European problem. By 2000, the number of confirmed cases of BSE were as follows; UK 1,337; France 138; Switzerland 33; Ireland 57; Portugal 136; Germany 7; Belgium 9[41]. The World Health Organisation (Fact Sheet No. 113) report that since 1989, cases have been reported in native cattle in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Japan, Liechtenstein, Luxembourg, Netherlands, Poland, Portugal, Slovakia, Spain and Switzerland.

Sporadic CJD in young people

There have been rare reports of sporadic CJD in teenagers in the literature. In 1981, Monreal et al reported the case of a sixteen-year-old boy from the USA, with a triad of progressive dementia, stimulus sensitive myoclonus, a characteristic EEG and a spongiform encephalopathy confirmed at post mortem[42]. Brown et al, 1985 describe a 19-year-old girl from France presenting with headaches, lethargy, somnolence, personality change, cognitive decline and a progressive cerebellar syndrome with myoclonus and abnormal movements[43]. EEG showed bilateral, symmetric 1-2 cycle per second pseudoperiodic sharp wave spike activity. Histological examination of a fragment of temporal cortex confirmed the presence of spongiosis, neuronal loss and reactive gliosis. There is a report from Canada, of a 14 year old, English born girl, with pathologically confirmed sporadic CJD, who presented with slowly progressive clumsiness, unsteady gait, personality change and cognitive decline[44]. Kulczycki et al report three young cases from Poland, one of whom was age 19, presenting with memory loss, confusion, and evidence of dementia, spasticity and tremor on examination[45]. There was pathological confirmation of a spongiform encephalopathy. However, these cases of CJD in teenagers were extremely rare, which increased the significance of the reporting of two cases of apparent sporadic CJD in teenagers in the UK in October 1995. Britton et al describe a 16-year-old girl who presented in 1994 with backache, numbness in the fingertips and face and subsequently, dysarthria, poor balance, clumsiness of the limbs and urinary frequency[1]. On examination, she had poor recall and dyscalculia. She was dysarthric, had an intention tremor of the left upper limb and gait ataxia. Initial MR imaging was reported as normal (early reports in vCJD may have overlooked an abnormality in the thalamus). An EEG was normal. Her cognition deteriorated and she developed myoclonus. A frontal brain biopsy

revealed spongiform change and numerous cortical plaques with an eosinophilic centre and a vacuolated rim. Immunohistochemistry was positive for prion protein. There were no known mutations detected in the prion gene. Bateman et al describe an 18-year-old male with a six-month history of memory loss, apathy and confusion[2]. He subsequently developed visual hallucinations, delusions of reference, and an excessive fear of water. There was also deterioration in his gait. On examination, he was disorientated in time, place and person, dysarthric, with myoclonus, pyramidal signs and ataxia. MR imaging of the brain was reported as normal (signal abnormality in early reporting in vCJD may have been overlooked) but an EEG showed generalised non-specific slow wave activity. The illness was rapidly progressive, with overall duration 9-12 months. Post mortem examination confirmed the presence of spongiform change, astrocytosis and neuronal loss, most severe in the deep grey structures. Screening for PRNP excluded all known mutations and direct sequencing of the open reading frame excluded novel coding mutations. Both of these cases were noted to be homozygous for methionine at codon 129 of the prion gene.

By April 1996, the CJD Surveillance Unit reported ten cases of CJD in young people in the UK, with the unusual young age of onset, clinical features that varied from those of sporadic CJD, the absence of EEG changes characteristic of sporadic CJD and a unique neuropathological profile[40]. It was proposed that these were cases of a "new variant" of CJD and raised the possibility that they could be causally linked to BSE.

Evidence for transmission of BSE to humans

There is evidence that PrP^{Sc} molecular types, distinguished by their physicochemical properties are responsible for the different forms of CJD. PrP^{Sc} types may differ in their primary PrP sequence, the degree of glycosylation of the molecule and the final tertiary structure or conformation. This variety can be illustrated in the different patterns seen on molecular analysis by Western blot. Two distinct clinical groups have been described in sporadic CJD i.e. those with a Type 1 banding pattern on Western blot, with homozygosity for methionine at codon 129 of PrP, and those with a Type 2 banding pattern, in a minority of MM cases and all MV and VV cases[27]. Types 1 and 2 are also seen in some iatrogenic cases, although a third type is seen in peripherally acquired (growth hormone associated) iatrogenic CJD cases. All of the cases of vCJD have been MM at polymorphic residue 129 of PrP and all cases were associated with a unique Type 4 banding appearance on Western blot with a characteristic pattern of glycosylation (vCJD had band sizes similar to type 3 CJD but had a very different pattern of band intensities).

Transmission studies of all types of PrPSc, in transgenic mice (expressing only human PrP, the transgene homozygous for valine at codon 129) and non-transgenic mice, have provided further evidence that the same prion strain causes BSE and vCJD[12, 26]. Almost all transgenic mice inoculated with PrPSc types reported in sporadic and iatrogenic CJD contracted disease with similar short incubation periods. Far fewer transmissions were seen in non-transgenic mice with longer and more variable incubations periods. In contrast to this transmission of vCJD to non-transgenic mice was far more efficient, albeit with long incubation periods and transmission to transgenic mice was much reduced with variable incubation periods. The transgenic

mice inoculated with vCJD also showed unusual clinical features. BSE transmitted efficiently to nontransgenic mice with long incubation periods. BSE transmission was demonstrated to transgenic mice but with very long incubation periods and the appearance of the unusual clinical features seen with the transmission of vCJD to this species. The patterns of neuropathology were very similar in the vCJD and BSE inoculated animals (variant CJD and BSE inoculated nontransgenic mice had PrP plaques and diffuse PrP deposition whereas transgenic mice had a pericellular pattern of immunostaining). Further analysis by Western blot showed that vCJD inoculated non-transgenic mice produced mouse PrPSc with type 4 strain patterns indistinguishable from BSE inoculated nontransgenic mice. Transmission of vCJD in transgenic mice produced type 4 like glycoform ratios but with different fragment sizes (type 2 PrPSc pattern) and these were termed type 5 (conversion of fragment size on passage in mice with a different genotype at codon 129 has been well documented). Bruce et al conducted transmission studies of sporadic CJD and vCJD to mice, looking for the BSE signature, based on incubation periods and pathology, only ever seen in transmissions from animals suspected or known to have been infected with BSE[11]. They report a striking similarity between the vCJD and BSE in the mice in terms of both incubation period and neuropathology. This is further evidence that the same prion strain is involved in both diseases.

Variant CJD

Epidemiology

Concerns for the possible spread of BSE to the human population led to the detailed analysis of epidemiological data for all forms of CJD in the UK. Comparison of data for sporadic CJD (1970-1996) showed that the yearly number of deaths from CJD rose from an average of 24.8 in the pre-BSE period 1980-84 to 33.6 in the period 1990-96[46]. One of the greatest increases was seen in the over 70-age group. It was thought that this increase might reflect improved case ascertainment in this group. It has been estimated that only about 4% of elderly patients dying with dementia come to autopsy and therefore that many cases of CJD may be potentially missed.

A European Union collaborative study of CJD was initiated, to identify any change in the epidemiological characteristics of CJD from 1993-1995, which may have resulted from exposure of the human population to BSE across Europe[47]. Data from the national registries of the UK, France, Germany, Italy, The Netherlands and Slovakia were compared and the overall annual mortality rate for CJD in Europe was shown to be 0.71 cases per million, with remarkable, relative consistency in mortality rates noted, both with time and between countries. The data confirmed a high relative incidence rate of CJD in the youngest age group (<39 years) in the UK, coinciding with the emergence of vCJD. The geographical distribution of vCJD has been analysed[48]. The incidence is higher in the north of the UK compared to the south (rate ratio north versus south 1.94). There is no evidence of a link with social class and attempts to link these data to those on the consumption of meat and meat products as recorded in the Household Food Consumption and Expenditure Survey and the Dietary and Nutritional Survey of British Adults have given inconsistent results. A

cluster of five cases has been confirmed in Leicestershire. Investigations by the local public health teams have led to suggestions that people in this area with vCJD were 15 times more likely to have purchased and consumed beef from a butcher who removed the brain from a cow compared with control group relatives who purchased meat from retailers where cross contamination was not a risk[49]. Attention has also been drawn to a further possible cluster of cases in Kent, all living within 50 km of two rendering factories[50]. It has been postulated that another possible route of infection in Kent may have been via drinking water abstracted less than 2 miles from one of these rendering plants[51]. There have also been studies to look at the possible increased risk of infection with CJD in people working with animals or animal products. Aylin et al studied the records from people dying aged between 20-74 years, during 1979 and 1996 in England and Wales, with occupations including butchers, abattoir workers, farmers, farm workers or veterinarians[52]. No increase in deaths from CJD or other dementias was found among these occupational groups.

Predicting the size of a future epidemic

There have been 121 deaths due to definite or probable vCJD to 31st December 2002. Predicting the size of the vCJD epidemic is very difficult as the number of people likely to be infected is unknown, there being no diagnostic test to detect subclinical infection, and the range of incubation period is similarly unknown. Any projections therefore have to rely on assumptions about these missing quantities. There are estimates that 450,000 infected cattle entered the food chain in the UK prior to the SBO ban in 1989 and a further 280,000 after the ban[53]. Estimates would have to take many factors into consideration such as, the infectiousness of various bovine tissues, the patterns of consumption of bovine products in the general population and the

efficiency of transmission of prions to humans via consumption of beef products. These limitations mean that very large numbers of infections cannot be ruled out[54]. The age distribution of the cases may be explained by either greater exposure, greater susceptibility to infection or shorter incubation periods in young people. It should also be considered that if incubation periods are very long, some infected people might not develop vCJD in their lifetime.

In one patient, prion protein was detected in an appendix removed in 1995, 8 months prior to onset of symptoms of vCJD[55]. In another case, no prion protein was detected in an appendicectomy specimen removed in 1990, 9 years before symptom onset[56]. The fact that prions could be detected in lymphatic tissue of a case with subclinical vCJD led to the proposal that this may be one way of determining the level of subclinical infection in the general population. Over 3000 specimens from surgically resected appendices and tonsils were screened for the presence of prion proein[56]. No tonsil or appendix specimens were positive for prion protein. Using the mathematical model generating epidemic scenarios consistent with age stratified disease incidence and assuming that the tests can detect infection in the last 75% of the incubation period (with 100% sensitivity and specificity), then the upper bound of the epidemic size is reduced from several million cases to approximately 150 000 cases by this negative result. However, if the test could only detect infection in the last 50% of the incubation period, then there is no reduction in the predictions of an uncertain but very large epidemic. Interpretation of the results is hampered by uncertainty as to what a negative result implies for the probability of future disease. A further screen of large numbers of tonsils and appendices for prion protein, to determine the number of people with preclinical vCJD has been performed[57]. One appendix specimen out of

8318 specimens showed lymphoreticular accumulation of prion protein with immunohistochemistry using monoclonal antibodies. This gives the estimated detectable prevalence of prion protein accumulation among people aged 10-50 (between 1995 and 1999) as 120 per million. The authors recognise that large-scale prospective screening of tissue from tonsillectomies is needed to give more precise data.

The National CJD Surveillance Unit monitors the incidence of and mortality from vCJD. The annual death rate from vCJD remained relatively constant up to the last quarter of 1998. The total number of deaths over the three years 1996-1998 was 35, but nine deaths occurred towards the end of 1998[58]. However, the most recent analysis of the increasing trend in deaths showed that the increase was not exponential and that it is now slowing[59]. The authors of this report support the need for continued surveillance as it is possible there may be future epidemics. The disease may still occur in those who are homozygous for methionine at codon 129 of the prion protein gene but within subgroups with longer incubation periods than have been seen so far. The disease may occur in those with other genotypes (VV or MV) or those infected with other strains of BSE. The transmission of vCJD between people following surgical procedures with contaminated instruments or from blood products also has the potential to alter the incidence of the disease and the disease phenotype may differ if the route of infection is different

Investigating the possible underascertainment of vCJD

One important factor to consider when assessing the possible size of a future epidemic of vCJD is the possibility of underascertainment of cases prior to the recognition of

the disease in 1995/96. This has been investigated in two large studies in England and Wales[60&61]. Majeed et al performed a structured review of the clinical records of 1485 people who died age 15-44 years in England during 1979-1996. Sufficient information was retrieved in 91% of cases to exclude CJD as the cause of death. It was therefore concluded that it was unlikely that significant numbers of cases were misclassified in this age group. Hillier et al studied all certified deaths (excluding external injury and poisoning) in residents of Wales aged 15-45, between 1985 and 1995[61]. Those considered to fall into the category of "Non-specific fatal disorders compatible with vCJD" (a category decided by a steering committee looking at which ICD-9 diagnoses might be compatible with a diagnosis of vCJD at any stage of the illness) were examined further. These illnesses included suicide, transport accidents, neurological diseases (including encephalitis, encephalomyelitis, cerebral degenerations manifest in childhood, degenerative dementias, extrapyramidal disease, spinocerebellar ataxia, anterior horn cell disease, diseases of the autonomic nervous system, multiple sclerosis, epilepsy and coeliac disease), psychiatric diseases (discussed in detail later) and those due to substance abuse. Clinical data were reviewed and histological tissue re-examined and no new cases of vCJD were detected supporting the view that vCJD was a new disease and not simply the result of better case ascertainment.

Since May 1997 there has also been active surveillance for patients younger than 16 years old with progressive intellectual and neurological deterioration (PIND) in the UK. This has taken the form of a card reporting system by consultant paediatricians with follow up of cases by telephone interviews or site visits[62]. This was set up due to concerns that children may develop the disease and that it may look different

clinically in a younger age group. The study has confirmed the presence of two cases of definite vCJD and one probable case in the three-year study period and surveillance continues.

Clinical features of variant CJD

Detailed reports of the neurological, psychiatric and investigative features of the first fourteen cases of variant CJD were published by Zeidler et al from the CJD surveillance unit[4&5]. The clinical features were noted to be distinct from those of other forms of CJD. First the mean age of onset was only 29 years (range 16-48 years) and the median duration of illness was long, at 14 months, compared to that expected with sporadic CJD (mean age of onset 65 years, median illness duration 4.5 months). Secondly, there was a preponderance of psychiatric symptoms, early in the illness course. Most cases were depressed, withdrawn and lethargic and insomnia and weight loss were common. Sensory disturbance was another striking early feature. These ranged from paraesthesia, dysaesthesia, pain or a sensation of coldness, particularly in the lower limbs and feet. Some cases suffered from memory loss or mild unsteadiness from an early stage in the illness but further neurological signs were usually not apparent for a median of 6.25 months. Ataxia, involuntary movements, marked cognitive impairment, and urinary incontinence were common leading to akinetic mutism, sometimes with cortical blindness. The illness was rapidly progressive once neurological features appeared with the mean delay from unsteadiness and becoming bedbound, approximately 6 months.

The most common clinical signs included cerebellar limb or gait ataxia. Other signs seen in isolation or in combination with these included involuntary movements

(chorea, myoclonus), pyramidal signs, rigidity, sensory symptoms, upgaze paresis and the appearance of primitive reflexes. Some cases were noted to have a longer prodrome of personality change and sensory disturbance before the appearance of neurological signs.

No patients showed the characteristic EEG patterns associated with sporadic CJD (periodic sharp wave complexes). However, 12 out of 14 cases did have abnormal EEG readings, with slow-wave activity that deteriorated as the illness progressed. No cases showed a leucocyte response in the CSF, although 4 out of 14 cases had a raised protein level. Oligoclonal bands were not detected in any samples. 2 out of 5 cases tested for protein 14-3-3 were positive. MR imaging was reported as normal in 8 out of 14 cases (in early cases of vCJD signal abnormality may have been overlooked in the thalamus). Four were reported to have mild generalised atrophy. Two cases had high signal on T2 weighted images in the posterior thalamus.

Diagnostic criteria for variant CJD

Diagnostic criteria for vCJD have been proposed, based on the analysis of 33 pathologically confirmed cases[63] (see appendix I for updated criteria from the Department of Health, February 2003). Neuropathology is currently mandatory for the diagnosis of definite vCJD. The sensitivity of the diagnostic criteria for probable vCJD lies between 64 and 77%, depending on the availability of MR imaging for review, with 100% specificity.

Cases of vCJD usually present with psychiatric symptoms. Indications of the true aetiology of the disease include limb pain or sensory symptoms, cognitive decline, or even visual symptoms. Often the diagnosis is not considered however, until the onset

of frank neurological signs e.g. ataxia, a median of 8 months into the illness and diagnosis may be particularly delayed if the prodrome of psychiatric features and personality change is prolonged. Unusual presentations of vCJD have been documented, for example, with a nocturnal seizure disorder[64], or with loss of taste and smell[65]. The importance of thorough investigation is paramount as the differential diagnosis is wide and includes treatable causes e.g. cerebral vasculitis, Wilson's disease and Hashimoto's encephalitis[66]. MR imaging is the most useful non-invasive investigation to date and is discussed in detail later. The presence of CSF 14-3-3 is a useful marker in the diagnosis of sporadic CJD. One study shows a correlation with a diagnosis of sporadic CJD with 94% sensitivity and 84% specificity[67]. However the test will not distinguish sporadic and variant forms and false negative results have been documented in definite cases of vCJD. This may have been partly due to suboptimally stored CSF samples[68].

Alternative aids to diagnosis vCJD are under investigation. For example, the detection of loss of respiratory sinus arrhythmia by simple high-resolution ECG recordings has been shown to successfully predict BSE infection in cows[69].

A recent retrospective case note review of the first one hundred cases of vCJD confirmed the dominance of psychiatric features in the early stages, including dysphoria, withdrawl, anxiety, insomnia and loss of interest. Interestingly, it was noted that a significant proportion did exhibit neurological symptoms within four months of illness onset (memory loss, sensory disturbance, ataxia and dysarthria) and that a certain combination of psychiatric and neurological symptoms and signs might expediate the diagnosis in a proportion of patients[70].

Tonsillar biopsy

A definite diagnosis of vCJD can only be confirmed by brain biopsy or post mortem examination. However since PrP is widely expressed outside the CNS, the biopsy of alternative, more accessible tissues has been investigated as a diagnostic investigation for vCJD. Necropsy samples of lymphoreticular tissues (tonsil, spleen and lymph nodes) from patients dying of CJD and tonsil biopsy samples from patients suspected to have the disease have been analysed by Western blot and immunohistochemistry techniques to detect PrPSc[71&72]. All lymphoreticular tissues obtained at post mortem from patients with confirmed vCJD were positive for PrPSc but not those from patients with other forms of CJD or control subjects. Tonsil biopsy tissue was positive in all eight patients with an adequate tonsil biopsy specimen and with confirmed or probable vCJD. The test was negative in all patients subsequently found to have alternative diagnoses. Although the importance of a negative test has not yet been fully explored and the stage at which PrPSc may be detectable in tonsil tissue is not yet known, this test has the potential to be a highly sensitive and specific test in advanced disease.

Neuropathology remains essential for the diagnosis of vCJD. Large fibrillary PrP amyloid plaques surrounded by a halo of spongiform change are characteristic of vCJD. Other characteristic features include spongiform change which is more pronounced often in the basal ganglia, abundant PrP deposition in the occipital cortex and cerebellar molecular layer with perineuronal and perivascular deposits, and marked thalamic gliosis [73]. Direct comparison of vCJD with Kuru shows some similarities and differences in neuropathology[74]. In Kuru, spongiform change,

astrocytosis and neuronal loss were more severe in the frontal cortex, hippocampus (CA1 area) and the cerebellum. In the caudate nucleus and putamen, these changes were of equal severity to those seen in vCJD. The type and distribution of PrP deposition were also similar in vCJD and Kuru. In the same comparison, it was noted that PrP deposition was often seen in well-preserved areas, with a tendency for proper plaques as well as diffuse deposits. Some of the plaques were multicentric in both diseases, but florid plaques were only rarely seen in Kuru.

STUDY I

Methods

Case selection

The study was nested within the comprehensive clinical assessment and diagnostic services for patients presenting with suspected pre-senile dementia to the National Hospital for Neurology and Neurology (NHNN) and the Prion Clinic at St. Mary's Hospital, London, the latter established shortly before commencement of the project. Between eight and seventeen confirmed new cases of all forms of prion disease have been seen at these two centres each year since 1998. Many more are assessed and alternative diagnoses reached. 15 cases of confirmed vCJD participated in the study over a four-year time period (May 1998 – May 2002).

Table 1 The number of cases of variant CJD assessed for the study with the total deaths from definite or probable variant CJD in the UK over the same time period.

Year	Number of new cases of variant CJD assessed	Deaths from definite or probable Variant CJD in the UK (CJD Surveillance Centre, Edinburgh)
1998 (From May)	5	8
1999	2	15
2000	2	28
2001	4	20
2002 (End May)	2	9

The number of new cases seen at the two centres, as a percentage of the deaths from definite and probable vCJD in the UK for each year, was therefore: 28% for 1998; 13% for 1999; 7% for 2000; 20% for 2001; 22% for 2002.

Both the NHNN and the St. Mary's Prion Clinic are national, tertiary referral centres. In the first year of the project, approximately 28% of the total national cases were seen at one of these two sites. This was lower than expected and this figure fell to 7% in 2000. The prion diseases are difficult to diagnose, particularly in the early stages of the illness as they often have an insidious onset. Lengthy investigations are often undertaken by referring hospitals to rule out other diagnostic possibilities, before variant CJD is considered. The rapid progression of psychiatric, cognitive and motor problems in young people with a delay in reaching a diagnosis is particularly distressing for relatives. By the time the diagnosis was discussed the relatives often felt that travelling a distance with their spouse or child, to a specialist centre, was a further unnecessary trial, if no treatment was available. With the formulation of diagnostic criteria for the disease, neurologists were able to make the diagnosis of vCJD with increasing confidence. Referral to the Prion Clinic was encouraged as this allowed a histological diagnosis to be made by tonsillar biopsy. This is particularly important, as post mortem is not compulsory for all cases of probable or possible vCJD.

During the first year of the study it became clear that referrals would be limited and cases were presenting with moderated to advanced disease. One way to increase the size of our control group would be to increase the index of suspicion amongst general practitioners, with a request to refer more young people with symptoms of depression and personality change. However, the complaints associated with these conditions were extremely common and it was considered inappropriate to worry vulnerable young people about a very rare illness where no treatment was available. Recruitment into the neuropsychology and imaging sections of the study was broadened to include

cases with familial and sporadic forms of prion disease referred to the centre. With hindsight it would have been informative to include a group of controls with young onset Alzheimer's disease (AD), as AD forms part of the differential diagnosis of vCJD.

The number of cases of vCJD referred to the NHNN and St. Mary's hospital did increase to 25% of the National figure in 2001 with the commencement of therapeutic trials for disease modifying agents.

Consent and ethical considerations

Ethics approval for all aspects of the study was obtained from the National Hospital Joint Ethics Committee (ref: 97/N076) and St. Mary's Local Research Ethics Committee. An information sheet was given to each subject and their next of kin prior to consent being obtained. Written consent was obtained from the subject if they were felt to be competent to understand the implications of the study. The assent of the next of kin was also sought. In the case of a child under the age of 16, consent of the subject and their next of kin were sought.

In accordance with the requirements of the Data Protection Act 1998, we informed all subjects that clinical details would be held on the UCLH NHS computer system. Anonymized research data were also held on a secure database, on a UCL system, with restricted access within the Dementia Research Group. Data were stored for the purpose of providing health care, and the research and statistical analysis outlined in the project.

Following the guidelines published by the General Medical Council concerning the publication of clinical data pertaining to patients with *rare* conditions, we further consulted the relatives of cases, at the end of the study, for consent to publish anonymized information. Consent was given in 11 cases; two declined and 10 were no longer contactable by telephone or post. There follows therefore, detailed description of 9 of the 21 cases enrolled. For the remaining cases, a tabulated summary of the clinical features is presented.

Inclusion criteria

All subjects referred to the NHNN and the Prion Clinic at St. Mary's Hospital, London, for the further investigation of possible variant CJD, were approached for entry into the study. A proportion of these cases, were ultimately given alternative diagnoses and therefore served as a control group in the analysis of the results of the psychiatric, psychology and imaging studies.

Further comparison is made with data collected from similar psychology and imaging studies performed in subjects referred to the centres with known familial, sporadic or iatrogenic CJD over the study period.

Clinical Data Collection

A detailed history was taken from each patient and their family. Multiple family members were involved to corroborate dates. The clinical notes were examined for extra information. A full general and neurological examination was performed. The

patient was classified as having probable or possible vCJD, if appropriate and a further working differential diagnosis was given. This quantity of clinical data was collected so that the clinical phenotype of vCJD could be established and compared to early reports in the literature. It was important to watch for unusual features of the disease. It was also important to be able to put the results of the psychiatric, neuropsychology and imaging studies into a clinical context for each patient. This allowed the suggestion of links between symptoms and signs and abnormalities found on neuropsychology testing and imaging.

Case Summaries

Patient V1

This 38-year-old gentleman presented with a 9-month history of, initially change in personality i.e. becoming short tempered and irritable with mood swings, depression of mood and insecurity. He later developed paranoid ideas of reference in relation to his work colleagues. His wife noticed involuntary jerky movements in his sleep that progressed to similar involuntary movements of the limbs whilst awake and he had complained of a sensation of heat and burning in his feet. The sensory symptoms progressed to involve both legs, face and scalp and to such an extent that he was unable to shave. Other features that developed included cognitive impairment, with noticeable difficulty with route finding in familiar environments, occasional incontinence of urine and problems with balance. By 11 months into the illness there were increasing problems with confusion and aggressive behaviour especially at night.

He was adopted and so had no information about his biological parents. He had two children by his first marriage, both well. He drank moderate amounts of alcohol and had recently given up a mild smoking habit. On systemic enquiry he had recently suffered with bouts of diarrhoea.

General examination was normal. The patient was restless, agitated and disorientated in time and place. His gait was broad based and mildly ataxic. There was some dystonic posturing of both feet with some choreiform movements, (which later became generalised). No myoclonus was seen during his inpatient stay (the history

suggested that this had been present previously). Examination of the cranial nerves was normal except for a mild orofacial dyspraxia and spontaneous speech appeared normal. Tone was increased in the lower limbs with some clonus at the ankle, power was normal. There was some hypersensitivity to pin prick sensation in both feet. There was heel-shin dysmetria in both lower limbs. There was symmetrical hyperreflexia with probable flexor plantar responses.

The complete open reading frame of the prion protein gene was sequenced and no mutations were detected. The codon 129-genotype was methionine homozygous. Western blot of tonsil tissue demonstrated $PrPS^c$ of the type seen in all other cases of vCJD. PrP immunohistochemistry was positive.

The patient died 14 months into the illness. At post mortem mild focal spongiform change was seen in the cerebral cortex (most marked in the occipital lobes) with scattered plaques, some "florid" in appearance. Spongiform change, gliosis and neuronal loss were marked in the globus pallidus, putamen, caudate nuclei and the thalamus. Immunocytochemistry showed extensive PrP deposition throughout the brain including the cerebellum. In the cortex, there were scattered discrete plaques and granular deposits. PrP deposition in the basal ganglia was prominent around vacuoles and in linear "beaded" chains. In the thalamus, there were granular and linear deposits and occasional plaques. There was also granular staining in the dorsal root entry zones and gracile columns of the spinal cord. The diagnosis of variant CJD was confirmed.

Patient V2

This 38-year-old gentleman presented with a 14-month history that began with sudden onset of back pain on holiday and no other symptoms. This was investigated by an orthopaedic team in the UK and tests included MR imaging. The pain persisted but changed in character over the next six months, radiating down the legs (right greater than left) and was not improved by an epidural. Further sensory symptoms developed, 10 months from the illness onset with tingling in both hands and feet, with the skin feeling raw as if being rubbed off. The pains extended into the face, head and abdomen and became increasingly severe. By 11 months from the illness onset, the patient had noticed some slurring of his speech and he was experiencing difficulty with walking, his right leg giving way, and some stiffness. Over this time it was noticed that he was increasingly short tempered and aggressive. He had been depressed as a consequence of his pain and had noticed some cognitive problems, with particular difficulty doing mechanical things or using equipment e.g. his mobile phone. He had an increased tendency to eat sweet things.

There was no family history of neurological problems or dementia. There was no past medical history of note.

The patient scored 17/30 on the mini mental state examination. His speech was slow and mildly dysarthric. Eye movements were broken with no nystagmus. There was stimulus sensitive myoclonus. His gait was broad based and ataxic. There was drift of the right arm and tone was increased particularly in the right leg. The reflexes

were brisk (it was not possible to elicit the plantar responses due to sensitivity of the feet). There was hypersensitivity to pinprick sensation in the lower limbs. There were no primitive reflexes.

The complete open reading frame of the prion protein gene was sequenced and no mutations were detected. The codon 129-genotype was methionine homozygous.

Western blot of tonsil tissue demonstrated $PrPS^c$ in a pattern seen with all other tested cases of variant CJD. Immunohistochemistry for PrP was also positive.

Patient V3

This 28-year-old woman presented with symptoms dating back 13 months, with initial behavioural change i.e. becoming increasingly short tempered and aggressive, and emotional lability. She was diagnosed with depression by her GP and treated with antidepressant therapy (fluoxetine, thioridazine and venlafaxine). She was also treated with antibiotics for swellings in her breast and groin. Six months later, her family noticed deterioration in her balance and walking. She went on to develop choreiform movements of her head and limbs, some slurring of her speech and amenorrhoea. Subsequent deterioration was rapid with disorientation in time and place, a childlike character, marked cognitive decline with an inability to read or concentrate on the television and urinary incontinence. Although she had not complained of any abnormal sensory symptoms, she would get very distressed if anyone attempted to touch her lower limbs.

There was no medical or surgical history of note. She smoked 20 cigarettes per day. There was no family history of neurological illness. On systemic enquiry, she had previously complained of occasional "panic attacks" with shortness of breath and palpitations.

The patient arrived in a wheelchair. General examination was unremarkable. There were marked choreiform movements of her head and limbs. No myoclonus was seen. She had a broad based gait with marked ataxia. Her right pupil was smaller than the left and poorly reactive. Eye movements were full with no nystagmus. There was some dyspraxia of eye opening and tongue movements. No primitive reflexes could be elicited. There was mild increased tone in the lower limbs. Power was intact. Coordination was poor in the lower limbs. Reflexes were symmetrical (it was not possible to test ankle reflexes and plantar responses due to hypersensitivity of the lower limbs). Sensation was intact, though it was not possible to test the lower limbs, again due to hyperpathia.

The entire open reading frame of the prion protein gene was sequenced and no mutations were detected. The codon 129-genotype was methionine homozygous. Western blot of tonsil tissue was positive for $PrPS^c$ in the pattern seen in other cases of variant CJD. PrP immunohistochemistry was also strongly positive.

The patient died 16 months from illness onset. At post mortem, on macroscopic examination of the brain, the lateral ventricles appeared minimally, evenly dilated. Sections of the frontal, frontoparietal, temporal and occipital lobes, basal ganglia,

thalamus, cerebellum and brainstem showed evidence of a spongiform encephalopathy. The most affected areas included the thalamus, hypothalamus, amygdala, frontal boundary zone, tectal plate, periaqueductal grey, substantia nigra, pontine tegmentum and the occipital cortex. In the neocortex, the rather patchy spongiform change was associated with oval prion amyloid deposits. The white matter was generally gliotic and there was fibrosis of the meninges. Prion immunohistochemistry was strongly positive. The neuropathological diagnosis of definite variant CJD was given.

Patient V8

This 13-year-old girl presented with a five-month history commencing with behavioural change and subsequent dysarthia and a progressive movement disorder. Her mother reported that she had an ingrowing toenail infection five months prior to this and a urinary tract infection that had led to her being "run down". She was becoming tired at school during the autumn term and finding it difficult to find the energy to do her homework. She seemed to have an abnormal fear of her teachers and feared going to school because she had not completed her homework. She developed a sudden onset of behavioural change in December of that year and was both verbally and physically aggressive to her family, throwing dangerous objects and using abusive language. There were no complaints from her school until February the following year, at which time she first complained that her legs felt "funny". Her family noted that her speech was slurred and gait unsteady. One of her teachers noted jerky movements. Over the subsequent two months her speech, handwriting,

cognition and balance deteriorated and she became childish, dependent and emotionally labile. She complained of bilateral leg pain and myoclonus was noted. She latterly had disturbed nights, often crying for long periods and had tactile and visual hallucinations. There was no past medical history of note. Her parents and older sister were all well. Her maternal grandfather was reported to have "fits" and an aunt, multiple sclerosis.

General examination was unremarkable. There were marked generalised chorea (upper limbs > lower limbs) and orobulbar movements. Eye movments were normal and the cranial nerves were intact. There was an intention tremor in the upperlimbs. Tone and power were normal. There was some past pointing in the upper limbs. Reflexes were symmetrical. The gait was ataxic and the patient could not sit or stand unaided.

The entire open reading frame of the prion protein gene was sequenced and no mutations were detected. The codon 129-genotype was methionine homozygous. $PrPS^c$ was demonstrated by Western blot of tonsil tissue and immunohistochemistry for $PrPS^c$ was positive.

Patient V10

This 25-year-old gentleman first developed symptoms, 11 months prior to referral to the Prion unit. His father noticed a change in his behaviour and personality around the time that he went on holiday with his long-term girlfriend and her children. His

father felt it was very out of character that he informed his girlfriend on the first day of their holiday that he was involved with another woman. He was depressed and complained of multiple physical problems e.g. pain in his arms, difficulty sleeping and difficulty passing urine. He was prescribed antidepressants by his GP but only took them for two weeks. Four months later he arranged a trip abroad and mixed up the bookings and became verbally aggressive to the airport staff. His father also remembers that he had to write down instructions on how to drive home when taking his father to hospital, as he could not remember the route by car. The patient had previously been active but was scuffing his feet when walking by this time and was mildly unsteady. There was a rapid deterioration after approximately 8 months of symptoms, and the patient needed help with all the ADLs including toileting.

There was a family history of polyposis coli and depression. His paternal grandmother had a psychiatric illness and died age 73 years. The patient had a moderate alcohol intake and was a nonsmoker, though he had possibly smoked cannabis at university.

General examination was unremarkable. The patient was orientated in person only. The patient was able to engage but with fluctuating attention. He had a vacant expression with chewing movements of the jaw (orofacial dyskinesia) and occasional dystonic movements and myoclonic jerks were seen in the upper limbs. Eye pursuit movements were broken and jerky, with gaze impersistence. There was an intention tremor. Tone was increased more prominently in the lower limbs, with clonus at the ankle. Power was full proximally (cooperation was poor with further testing).

Coordination was mildly impaired in the upper limbs. Reflexes were brisk with extensor plantar responses. There was no evidence of hypersensitivity in the limbs.

The complete open reading frame of the prion protein gene was sequenced and no mutations were found. The codon 129-genotype was methionine homozygous.

Western blot of tonsil tissue was positive for $PrPS^c$ in the pattern seen in other cases of variant CJD. PrP immunohistochemistry was also positive.

Patient V14

This 19-year-old gentleman was referred to the Prion unit with 18 months of symptoms. With hindsight there may have been a suggestion of deterioration in his work and handwriting in particular and he was struggling with maths. His friends noticed that his football skills had deteriorated over the next few months. His father really noticed a change about four months after this when he seemed to go "off balance" and to stagger when walking. The patient also complained of dizziness when going down stairs at school. He was admitted to hospital for investigation and he decided to defer his A levels. Over the next few months his speech deteriorated with word finding difficulties in particular. He had frequent awakenings from sleep, screaming, vivid dreams and occasional hallucinations. He complained of seeing people outside the window or people coming to beat him up. Over this time motor function deteriorated. He developed a tremor in both hands then jerky movments. Walking became increasingly difficult, and he used a wheelchair, 10 months from

illness onset. Six months prior to this assessment he developed dysphagia and by the time of admission he required NG feeding and was doubly incontinent. The patient had a hernia operation age 7. There was no family history of neurological illness. The patient was mute and drowsy. He was seated in a wheelchair with a head support and required a hoist to transfer. He was not able to cooperate with the examination and attempted to grab an approaching tendon hammer. He had hypomimic facies. There was difficulty following movements with his eyes. Tone was generally increased in the limbs. There were spontaneous slow movements of all four limbs (left>right). Myoclonic jerks had been previously documented. Tendon reflexes were present and brisk with flexor plantar responses. Abdominal reflexes were absent.

The complete open reading frame of the prion protein gene was sequenced and no mutations were found. The codon 129-genotype was methionine homozygous. Western blot of tonsil tissue was positive for $PrPS^c$ in the pattern seen in other cases of variant CJD. PrP immunohistochemistry was also positive.

Patient V15

This 21-year-old woman presented with a nine-month history of initially malaise, and behavioural change. Her parents described her as argumentative, irritable and over tired, which was out of character and they encouraged her to visit her GP. Over the next few months she complained of aching legs and a cold left foot. By six months her walking and coordination had deteriorated. Her parents went on holiday for two weeks that highlighted her inability to look after herself and prompted an emergency

admission to hospital. She further developed emotional lability, cognitive problems, dysarthria and choreiform movements. She had a past medical history of tonsillitis. She smoked 10 cigarettes per day and did not drink alcohol. There was no family history of neurological illness.

The patient was emotionally labile, with a cheerful affect but bursting into tears intermittently. She was orientated in all but place. General examination was unremarkable. No abnormalities were detected on cranial nerve examination. Tone was increased in the lower limbs with clonus at both ankles (L>R). Power was preserved. Coordination was reduced in the upper and lower limbs. Tendon reflexes were symmetrically brisk with positive finger jerks and extensor plantar responses. There was patchy reduction of pinprick sensation (left lower leg and L3, right lower leg, right arm). Gait was broad based and unsteady.

The complete open reading frame of the prion protein gene was sequenced and no mutations were found. The codon 129-genotype was methionine homozygous.

Western blot analysis and PrP immunohistochemistry of a tonsil tissue specimen were both positive.

Patient O1

This 36-year-old woman was noted by her family to have personality change, about seven years ago. She became apathetic and indifferent, stopped doing the household

chores for fear of contamination and performed obsessional rituals. A long-term relationship broke up about five years ago and she moved to live with her brother. About one year later she returned to her home area but was unable to cope with a house and moved to a flat. Her obsessional behaviour had, by this time disappeared. Over the last two years she had become increasingly reclusive and her GP prescribed antidepressants. Approximately eighteen months ago she developed poor balance with a tendency to fall to the right, and occasional twitching of the limbs. Her condition progressed such that she became increasingly emotionally labile, incontinent of urine and faeces, and complained of spasms in her legs. She had been in a nursing home for one year at the time of referral.

She had a road traffic accident age 17, in which her boyfriend died. She suffered a head injury with concussion. She cut her arms for two years following this and "drifted" for a while, with periods of heavy drinking and taking drugs. There is no family history of any neurological illness.

The patient was in a wheelchair and was cheerful and engaging. She scored 9/30 on the MMSE. General examination was unremarkable. There were frontal release signs and prominent dyspraxia. She had limited upgaze with impaired voluntary saccades and jerky horizontal pursuit movements. She was dysarthric and her tongue movements were slow and hesitant. There was generalised myoclonus and stimulus sensitive myoclonus. Tone was increased in all four limbs, legs>arms, with extrapyramidal rigidity and a spastic paraparesis. Power was normal in the upper limbs. There was bilateral finger nose ataxia. Reflexes were brisk but symmetrical, with extensor plantar responses. There was frontal executive dysfunction.

The complete open reading frame of the prion gene was sequenced and a mutation, P105L, was found. This is usually associated with a GSS "spastic paraparetic" phenotype. The codon 129--genotype was valine homozygous and there was a polymorphism at codon 209, which, to current knowledge, has no known affect on the disease phenotype. A diagnosis of familial CJD was given.

Patient O2

This 39-year-old female first developed episodes of blurred vision and mild photophobia, 7 months prior to assessment. About one month later, mild unsteadiness was noted which gradually progressed over the next few months, with the development of dysarthria and memory loss. There was some fluctuation in the severity of symptoms and the patient was often worse when tired. She found it hard to get up in the morning, became restless and lost her appetite. After six months of symptoms there was a more rapid deterioration in mood and behaviour, with dysarthria, abnormal eye movements, marked ataxia, cognitive decline and possible paranoid beliefs. Over the four weeks, prior to assessment at St. Mary's hospital, she stopped speaking and walking and became more jerky and incontinent.

There was a past history of tonsillectomy. Her father had died aged 76 after a twenty-year illness starting with dysarthria, ataxia and nystagmus and progressing to an ataxic, wasted, areflexic state. Her paternal grandmother had a possible diagnosis of

motor neurone disease with cerebellar degeneration and a paternal uncle may have been ataxic.

General examination was unremarkable. The patient was mute but could sometimes obey commands. Her eyes were open with roving movements and there may have been a supranuclear gaze palsy. Her face was impassive with some facial twitching and she had brisk facial reflexes. Tone was mildly increased in the limbs and there were some jerky movements. The tendon reflexes were brisk and symmetrical and the plantar responses were flexor.

The complete open reading frame of the prion protein gene was sequenced and no mutation was found. The codon 129-genotype was valine homozygous.

Tonsillar biopsy was not performed due to systemic sepsis.

The patient died 15 months from symptom onset. At post mortem macroscopically there was severe diffuse atrophy, including the cerebellum but with relative preservation of the occipital lobes. On microscopic examination the changes were extreme with some unusual features. There was severe degeneration of both the grey and white matter. Both the cortex and deep grey matter were affected. The white matter showed marked degeneration and extensive loss of myelin. Prion deposition was extensive in the grey and white matter. There was a diffuse punctuate deposition in association with vacuolation in the cortex, dense deposits resembling plaques were also noted and fine granular deposition within the cells. Dense deposits of varying sizes were seen in the white matter. There were no florid plaques.

A diagnosis of sporadic CJD was given.

Patient O6

This 35-year-old, righthanded gentleman was assessed at the NHNN after a 13-month history starting with intermittent myoclonic jerks of the upper and lower limbs and head. He had a generalized tonic-clonic seizure four months later and since that time the myoclonic jerks increased in frequency. Around this time he also complained of memory impairment, behavioural disturbance and emotional lability. Subsequently he had cramping dysaesthesiae and paraesthesiae of the lower limbs and a couple of months prior to assessment his walking became unsteady. His myoclonic jerks responded well to treatment with sodium valproate and clonazepam and his cognitive impairment was relatively unchanged. He had several absence seizures a week and his walking deteriorated to the point that he needed a walking stick. He was recently diagnosed with diabetes mellitus. His mother (age 75) has a diagnosis of probable Alzheimer's disease. There is no other family history of note. The patient had pneumonia as a child and a tonsillectomy. He is a smoker and drinks little alcohol.

On general examination the patient was noted to be overweight, with bilateral ptosis and myopathic facies. There was mildly limited abduction of the left eye and saccadic intrusions on horizontal pursuit and hypometric saccades. There was a mild tremor of the hands and mild ataxia of the left upper limb. Reflexes were normal apart from a depressed left ankle jerk. Plantar responses were flexor. The gait was mildly ataxic. He scored 28/30 on the MMSE.

A tonsil biopsy was not performed. The codon 129-genotype was methionine homozygous.

Microscopic examination of a skin biopsy revealed round subnuclear intracytoplasmic inclusions in several of the myoepithelial cells surrounding the apocrine glands. The inclusions stained with PAS and Lugols stain. Electron microscopy showed occasional intracytoplasmic inclusions, consisting of fibrillary material and non-encapsulated.

Diagnosis: Lafora Body disease.

Patient O7

This 25-year-old, Caucasian gentleman presented 14 months prior to assessment with an acute onset schizophreniform psychosis. He initially reported feeling "stressed out" and took several weeks off work, but on returning to work he was promptly sent back home being described as vacant, and making mistakes, such that he could not perform his job as a warehouse man properly. Approximately two months later, he went away for a long weekend with a friend and took cocaine, drank alcohol and smoked cannabis. His mother reports that he was markedly different on his return, with paranoid beliefs, for example believing that passers-by and neighbours were out to do him harm. He was observed to have conversations with the TV and a mobile phone that was not connected. He complained of second person auditory and visual hallucinations. He exhibited bizarre behaviour, such as carrying around a scarecrow,

which he explained was his soulmate. His sleep was reduced to 1-3 hours per night. His behaviour became increasingly agitated and threatening.

He was admitted to a psychiatric ITU and treated with chlorpromazine and droperidol. As an inpatient he was noted to have frequent fits, starting with repetitive twitching of the right hand, with a slow Jacksonian march of the right arm, followed by his eyes rolling up and his head being thrown back and loss of consciousness. On one occasion, clonic movements of the legs were noted. Carbamazepine was commenced with little effect, followed by zuclopenthixol and procyclidine and later olanzapine and sodium valproate. His behaviour became increasingly withdrawn; he stopped eating and displayed self-injurious behaviour. He had some response to ECT.

After about five months of symptoms, he was transferred to another hospital, with a coincident improvement in his behaviour. His self-care, eating and drinking normalised and his behaviour normalised. Seizure control also improved with sodium valproate. The patient was initially discharged five months later, but his mother found his insomnia, disorientation and memory disturbance difficult to manage. There was evidence of a continuing psychosis, with sexual disinhibition and he was readmitted to hospital.

There was a past medical history of psoriasis age 13 and idiopathic thrombocytopenic purpura age 15, treated with steroids. The patient regularly smoked cannabis. He sniffed 1 gram of cocaine at weekends, for five years. He regularly took ecstasy tablets and had also tried LSD and amphetamines.

The patient obeyed simple commands but only spoke a few words, tending to perseverate. There was severe cognitive impairment. His eye movements were full, although the saccades were rather slow. There was possible visual distortion. He was not ataxic and could walk unaided. Tone in the limbs was normal, with power preserved. The reflexes were brisk and the plantar responses were extensor.

The complete open reading frame of the prion protein gene was sequenced and no mutations were found. The codon 129-genotype was methionine homozygous.

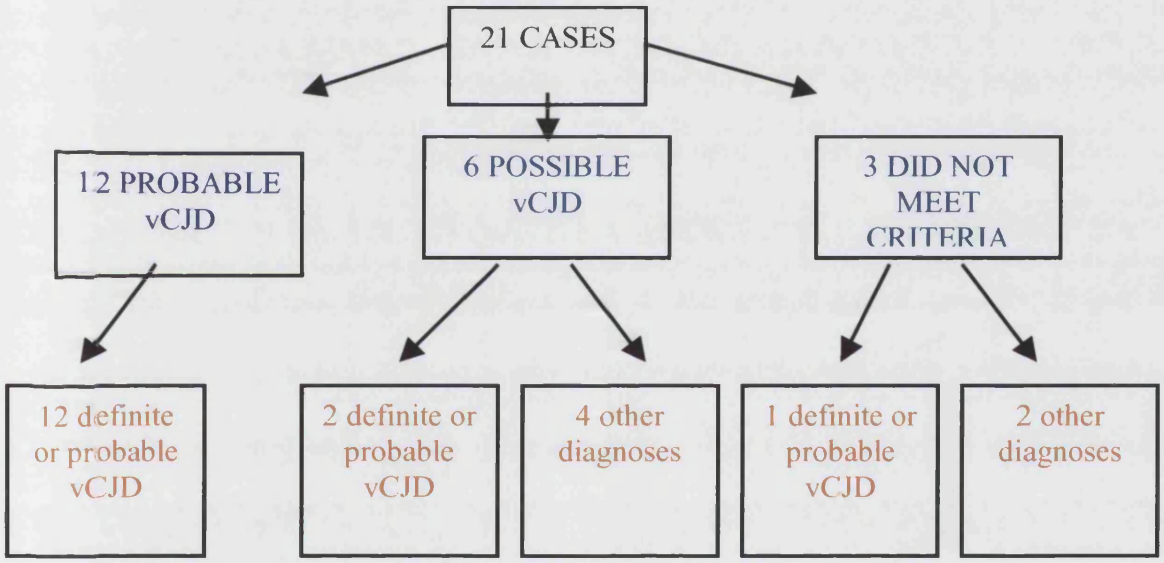
Western blot analysis of tonsil biopsy material was negative for PrPSc. Immunohistochemistry for PrPSc was negative.

The patient continues to need treatment for psychotic symptoms but no longer requires anti-convulsants. His cognitive decline was at its worse at the time of review for the project with slow but definite improvement since then. The aetiology of his illness remains unclear despite extensive investigations. A diagnosis of a post-encephalitic illness of unknown aetiology is most likely.

Results

Summary of the main clinical findings.

23 patients with suspected vCJD were enrolled into the study. One family withdrew their consent for publication of data and one case was followed up elsewhere. Therefore 21 subjects completed participation in the study. Diagnostic criteria for vCJD were applied on *entry* into the study (all cases had had previous MR imaging and EEG examinations at their referring hospitals). 12 of the 21 cases were classified as probable vCJD, 6 possible and 3 did not meet criteria for vCJD at this stage.



(Blue text = classification of disease on entry into study; Orange text = final classification)

Fifteen cases were confirmed as vCJD by tonsillar biopsy, 9 female and 6 male. The mean age at illness onset was 26 years for the female cases and 29 years for the males. The average duration of the illness at the time of assessment was 13 months. In the control group, 6 cases were reported where vCJD was not the final diagnosis. The mean age at illness onset in this group was 32 years for the females and 35 years for

the male cases. The mean duration in months of the illness at the time of assessment was longer in this group at 26 months (tables 2,3 and 4).

It was realised that the control group would be small (n=6) with varied diagnoses, which would not permit the meaningful application of statistics for comparisons with the patient group. The control group was therefore expanded, as explained in the methods, for the imaging and neuropsychology parts of the study.

Fourteen of the fifteen cases with vCJD presented, in the first instance to their GP. One case mainly involved hospital physicians/ surgeons (A& E and orthopaedics). Four cases were referred to a psychiatrist prior to a neurologist, at a mean of 10 months from illness onset. Five out of the 15 cases saw a psychiatrist at any time. All cases were referred to a neurologist at some time in the illness course, at a mean of 11 months from illness onset. The mean time to confirming the final diagnosis by tonsil biopsy was 14 months (tables 19 and 20).

Six out of the 15 cases of vCJD complained of symptoms of depression at presentation and 10 out of 15 during the first four months of the illness. Personality change was noted initially in 8 out of 15 cases, and in 11 out of 15 cases within four months. Three of these cases complained of cognitive problems from the outset and in seven cases this was an early feature (within 4 months). Complaints of difficulty walking or with poor balance were made by four cases at presentation, and seven by four months. Other symptoms complained of at presentation included sensory disturbance in seven cases, two cases with altered vision and six with sleep abnormalities. By comparison, four of the six cases with alternative diagnoses had

personality change as an early feature, although only two had symptoms of depression and only two complained of cognitive problems. Two of the cases had balance problems. Two cases complained of headaches and one of these had some numbness in one hand. However, none of this group complained of dysaesthesiae or hyperaesthesia. One case had altered vision and another sleep abnormality early on in the illness course (tables 5 and 6).

Symptoms progressed such that all cases of vCJD developed cognitive problems and cerebellar ataxia and 11 out of 15 noted sleep abnormalities. Similarly, 6 out of 6 testable cases in the control group developed cognitive problems, 4 out of 6 balance problems and 6 developed sleep abnormalities (tables 7 and 8).

In the fifteen confirmed cases of vCJD, thirteen developed ataxia, twelve had pyramidal signs but none showed the extrapyramidal signs of bradykinesia, postural disturbance or rigidity. Extrapyramidal involunatary movements were seen; six out of 15 had myoclonus, ten had chorea and four had dystonic posturing. Two cases had an upgaze paresis. In the control group of six cases, two had ataxia, five out of five cases that could be examined had pyramidal signs and one had extrapyramidal rigidity. Three out of six cases had myoclonus, none had chorea and one case had an upgaze paresis (tables 9 and 10).

Results of the main investigations are summarised in tables 11-18. MR images were reviewed for all cases. No cerebral atrophy was visible on inspection of the cases with probable vCJD. Fourteen out of the sixteen cases with confirmed vCJD had increased signal change in the posterior thalamus on T2 weighted images. Increased

signal was also seen in different cases in the head of the caudate nucleus, the upper midbrain, the parietal cortex and subcortical areas, the centrum semi-ovale, the cortical white matter, the middle thalamus and the occipital white matter extending into the globus pallidus on the right. In the control group, one case showed global cerebral and cerebellar atrophy. No signal change was seen in the posterior thalamus but one case had altered signal in the mesial frontal lobes and another in the caudate and lentiform nuclei.

For an overview of the clinical symptoms, signs and investigations see tables 5-20. These data are discussed in the context of the psychiatric features, neuropsychology profiles and imaging characteristics in the following chapters.

Table 2: Assessment stage, confirmed cases of variant CJD

Subject	Assessment Stage (x mths into illness)
V1	10
V2	14
V3	13
V4	13
V5	16
V6	25
V7	12
V8	13
V9	11
V10	10
V11	10
V13	13
V14	18
V15	9
V16	20

Table 3: Assessment characteristics, alternative diagnoses

Subject	Assessment Stage (x mths into illness)
O1	84
O2	8
O4	24
O5	9
O6	14
O7	16

Table 4: Final alternative diagnoses

Subject	Final diagnosis
O1	familial CJD
O2	sporadic CJD
O4	familial CJD
O5	sporadic CJD
O6	Lafora Body disease
O7	psychotic illness

Table 5: Presenting symptoms, confirmed cases of variant CJD

Subject	Early Symptoms < 4 months							
	Depression	Change in personality or behaviour	Cognitive problems	Cerebellar (ataxia or dysarthria)	Paraesthesiae or numbness	Dysaesthesiae	Altered vision	Sleep abnormal or malaise
V1	+	+	+	-	-	+	-	+
V2	+	+	-	+	+	+	-	-
V3	+	+	-	-	-	-	-	-
V4	+	+	-	-	-	-	-	-
V5	+	+	+	-	-	-	-	-
V6	+	+	-	-	-	-	-	-
V7	-	+	+	-	+	+	-	-
V8	-	+	-	-	-	-	-	+
V9	+	+	-	+	+	+	+	+
V10	+	+	+	+	-	+	-	+
V11	-	-	+	+	+	-	-	-
V13	+	-	+	+	+	-	+	+
V14	-	-	+	+	-	-	-	-
V15	-	-	-	+	+	-	-	+
V16	+	+	-	-	-	-	-	-

Table 6: Presenting symptoms, group with alternative diagnoses

Subject	Early Symptoms < 4 months							
	Depression	Change in personality or behaviour	Cognitive problems	Cerebellar (ataxia or dysarthria)	Paraesthesiae or numbness	Dysaesthesiae or headache	Altered vision	Sleep abnormal or malaise
O1	+	+	-	-	-	-	-	-
O2	-	-	+	+	-	-	+	-
O4	+	+	-	-	-	+	-	+
O5	-	+	+	+	-	+	-	-
O6	-	-	-	-	-	-	-	-
O7	+	+	+	-	-	-	-	-

Table 7: Symptoms experienced throughout the course of the illness, confirmed cases of variant CJD

Subject	All Symptoms							
	Depression	Change in personality or behaviour	Cognitive problems	Cerebellar (ataxia or dysarthria)	Paraesthesiae or numbness	Dysaesthesiae	Altered vision	Sleep abnormal or malaise
V1	+	+	+	+	-	+	-	+
V2	+	+	+	+	+	+	-	+
V3	+	+	+	+	+	+	-	+
V4	+	+	+	+	-	+	+	+
V5	+	+	+	+	-	-	-	-
V6	+	+	+	+	+	+	-	+
V7	-	+	+	+	+	+	-	-
V8	-	+	+	+	-	-	-	+
V9	+	+	+	+	+	+	+	+
V10	+	+	+	+	-	+	-	+
V11	-	-	+	+	-	-	-	+
V13	+	-	+	+	+	+	+	+
V14	-	+	+	+	-	-	-	+
V15	-	+	+	+	-	+	-	-
V16	+	+	+	+	-	-	-	-

Table 8: Symptoms experienced throughout the course of the illness, group with alternative diagnoses

Subject	All Symptoms							
	Depression	Change in personality or behaviour	Cognitive problems	Cerebellar (slurred speech or poor balance)	Paraesthesiae or numbness	Dysaesthesiae or headache	Altered vision	Sleep abnormal or malaise
O1	+	+	+	+	-	-	-	+
O2	+	+	+	+	-	-	+	+
O4	+	+	+	+	+	+	-	+
O5	-	+	+	+	-	+	-	+
O6	-	+	+	-	+	-	-	+
O7	+	+	+	-	-	-	-	+

Table 9: Clinical signs, confirmed cases of variant CJD

Subject	Clinical signs							
	Myoclonus	Chorea	Dystonia	Ataxia	Pyramidal	Extrapyramidal*	Upgaze paresis	Sensory abnormality
V1	-	+	+	+	+	-	-	+
V2	-	-	-	+	+	-	-	+
V3	-	+	-	+	-	-	-	+
V4	+	+	+	+	+	-	-	-
V5	+	+	-	NT	+	-	-	-
V6	-	+	-	+	+	-	+	+
V7	-	+	-	+	-	-	-	+
V8	-	+	-	+	-	-	-	NT
V9	-	-	-	+	+	-	-	-
V10	+	-	+	+	+	-	+	-
V11	+	+	-	+	+	-	-	+
V13	-	-	+	-	+	-	-	-
V14	+	+	-	+	+	-	-	NT
V15	-	+	-	+	+	-	-	+
V16	+	-	-	+	+	-	-	NT

NT = Not tested or unable to test; *extrapyramidal signs excluding involuntary movements (myoclonus, chorea and dystonia)

Table 10: Clinical signs, cases with alternative diagnoses

Subject	Clinical signs							
	Myoclonus	Chorea	Dystonia	Ataxia	Pyramidal	Extrapyramidal	Upgaze paresis	Sensory abnormality
O1	+	-	-	NT	+	+	-	-
O2	+	-	-	NT	+	-	+	NT
O4	-	-	-	+	+	-	-	-
O5	+	-	-	+	+	-	-	NT
O6	-	-	-	-	+	-	-	-
O7	-	-	-	-	NT	NT	NT	NT

NT = Not Tested or unable to test

Table 11: CSF examination, confirmed cases of variant CJD

	mths from illness onset	protein g/l	glucose (serum) mmol/l	cell count	oligoclonal bands	S100 ng/ml	NSE	P14-3-3
V1	9	0.48	4.8 (5.8)	0	0	na	na	na
V2	na	na	na	na	na	na	na	na
V3	13	0.57	3.1	1	0	1.36	45	positive
V4	13	0.20	3.7 (5.6)	1	na	0.92	22	trace
V5	8	1.60-2.90	normal	0	0	0.69	16	positive
V6	24	normal	normal	1	0	na	na	positive
V7	11	0.34	3.0 (4.8)	0	na	0.61	na	negative
V8	12	0.23	3.5	0	na	1.42	na	negative
V9	11	>3.00	normal	0	0	0.82	15	positive
V10	8	0.27	3.3	0	na	0.59	nt	negative
V11	9	0.75	normal	0	1†	0.33	18	negative
V13	13	normal	normal	0	0	0.55	na	negative
V14	5	0.40	3.7(4.4)	0	0	0.40*	na	negative*
V15	9	0.25	3.9 (5.4)	0	0	0.31	12	trace
V16	11	0.61	4.0	2	+ serum/CSF	0.4	12	negative

*na – not available; * 9 months later; † one unmatched CSF IgG band; +matched serum & CSF bands*

Table 12: CSF examination, cases with other diagnoses

	mths from illness onset	protein g/l	glucose (serum) mmol/l	cell count	oligoclonal bands	S100 ng/ml	NSE	P14-3-3
O1		na	na	na	na	na	na	na
O2	8	normal	normal	0	0	43	98	positive
O4	23	normal	normal	0	0	na	na	na
O5	7	0.97	3.1	0	0	0.88	35	positive
O6	8	0.53	normal	0	+serum&CSF	0.53	12	negative
O7	12	0.67	3.5	rcc<5;wcc<5	na	raised	nt	trace

na = not available; rcc = red cell count; wcc = white cell count; +matched serum and CSF bands

Table 13: MRI examination, confirmed cases of variant CJD

	mths from illness onset	atrophy		signal change	
		cerebrum	cerebellum	posterior thalamus	other
V1	7	0	0	0	0
V1	9 (DWI)	0	0	1	1 (head caudate)
V2	14	0	0	1	1 (upper midbrain)
V3	13	0	0	1	0
V4	11	0	0	1	0
V5	8	0	0	1	1(subcortical white matter lesions)
V6	22	0	0	1	0
V7	11	0	0	1	0
V8	15	0	0	1	0
V8	16	0	0	1	1(aqueduct,caudate, putamen bilaterally)
V9	11	0	0	1	1 (centrum semi-ovale)
V10	10	0	0	1	infarct left trigone
V11	9	0	0	1	1 (cortical white matter)
V13	13	0	0	1	1 (medial thalamus)
V14	16	0	0	1	1(medial thalamus)
V15	9	0	0	0	1 (occipital white matter, into globus pallidus R)
V16	9	0	0	1	0

DWI = Diffusion Weighted Imaging

Table 14: MRI examination, other diagnoses

	mths from illness onset	atrophy		signal change	
		cerebrum	cerebellum	posterior thalamus	other
O1	84	1	1	0	0
O2	8	0	0	0	0
O4	23	0	0	0	1 (mesial frontal lobes)
O5	9	0	0	0	1 (caudate and lentiform nuclei)
O6	8	0	0	0	0
O7	12	0	0	0	1(occipital horns)

Table 15: EEG examination, variant CJD cases

	mths from illness onset	periodic complexes	epileptiform activity	
V1	7	0	0	Disorganised background activity. Diffuse slow wave excess and irregular waveforms.
V1	9	0	0	Normal background activity. Intermittent excess theta over both hemispheres.
V2	14	0	0	Normal record
V3	13	0	0	Marked and diffuse slow activity over both hemispheres.
V4	10	0	0	Bilateral slow wave activity
V4	13	0	0	Non-specific mild to moderate disturbances.
V5	8	0	0	Bilateral slow wave activity
V6	22	0	0	Polyrhythmic low amp. Background, excess of fast act., increase of intermittent slow act..
V7	11	0	0	Normal.
V8	15	0	0	Diffuse slow activity, featureless periods, attenuated background.
V9	11	0	0	Widespread non-specific abnormality.
V10	10	0	0	Slowing of background rhythm, runs of sharp waves intermittently.
V11	9	0	0	Normal.
V13	15	0	0	No alpha rhythm, EEG dominated by theta and slow activity.
V14	16	0	0	Diffuse and nonspecific excess of slow and theta without definite alpha rhythm.
V15	9	0	0	Nonspecific abnormalities with widespread theta rhythms.
V16	9	0	0	Diffuse theta waves and periodic generalised delta waves.

Table 16: EEG examination, other diagnoses

	mths from illness onset	periodic complexes	epileptiform activity	summary
O1	84	0	0	normal
O2	8	0	0	nonspecific, mildly abnormal
O4	23	0	0	nonspecific excess of theta activity
O5	9	0	0	anterocentral excess of slow activity. Mild excess theta and slow widespread over cerebrum.
O6	8	0	0	mild and diffuse slowing
O7	14	0	0	Diffusely slow background with theta and delta activity.

Table 17: Biopsy and histology, variant CJD cases

	WB	IH	Frontal	Parietal	Temporal	Occipital	Thalamus	Globus Pallidus	Putamen	Caudate	Cerebellum	Brainstem	Spinal Cord
V1	+	+	S,F,P	S,F,P	S,F,P	S,F,P	S,G,N,P	S,G,N,P	S,G,N	S,G,N	P	P	P
V2	+	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
V3	+	+	SP	SP	SP	SP	SP	S	S	S	SP	SP	
V4	+	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
V5	nt	+	S,F,P	S,F,P	S,F,P	S,F,P	G,N,F,P	F,P	F,P	S,F,P	S,F,P		
V6	+	+	nt	nt	nt	nt	nt	nt	nt	nt	S,F	P	P
V7	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
V8	+	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
V9	+	+	S,G,N,F,P	S,G,N,F,P	S,G,N,F,P	S,G,N,F,P	S,G,F,P	S,P	S,P	SC,PP	S,N,F,P	S	
V10	+	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
V11	+	+	S,G,N,F,P	S,G,N,F,P	S,G,N,F,P	S,G,N,F,P	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P	S,N,F,P	S,N,G,P	
V13	+	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
V14	+	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
V15	+	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
V16	+	+	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt

WB – Western Blot; IH – Immunohistochemistry; S – Spongiform change; F – Florid plaques; P – Prion protein deposition; G – Gliosis; N – Neuronal loss; nt – not tested as no post mortem

Table 18: Biopsy and histology, other diagnoses

	WB	IH	Frontal	Parietal	Temporal	Occipital	Thalamus	Globus Pallidus	Putamen	Caudate	Cerebellum	Brainstem	Spinal Cord
O1	nt	nt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
O2	nt	nt	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P	S,G,N,P
O3	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
O4	nt	nt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
O5	-	-	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt	nt
O6	nt	nt	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
O7	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

WB – Western Blot; IH – Immunohistochemistry; S – Spongiform change; P – Prion protein deposition; G – Gliosis; N – Neuronal loss; nt – not tested as no post mortem;

NA- not applicable (still alive)

STUDY IA: A STUDY OF THE PSYCHIATRIC MANIFESTATIONS OF CJD

Introduction

The psychiatric features of CJD have been recognised for many years. In sporadic CJD, original large-scale studies of the clinical features have confirmed the presence of prodromal symptoms in 39% of "typical cases", consisting of asthenia, weight loss and sleep disorders, with two thirds showing some mental deterioration at the onset[75]. 94% show evidence of dementia, 45% behavioural change and 39% deficits of higher cognitive function as the disease progressed. Will et al classified three presentations of sporadic CJD, sub-acute, intermediate and an amyotrophic form[76]. In the sub-acute form, 33% had a prodrome of altered personality, or malaise with some anorexia and weight loss, with less frequent sleep disturbance. In 29% of cases, depression or emotional lability led to psychiatric referral. In fact at presentation, the commonest symptoms were of dementia (21%) and behavioural disturbance (18%), with visual hallucinations occurring in just 1%. Throughout the course of the illness, 17% experienced visual hallucinations and 100% developed dementia.

However, these "typical" cases of sporadic CJD are easier to diagnose and Will et al noted that it was the intermediate cases that caused problems i.e. 2 young cases presenting with emotional lability and ataxia and one presenting with personality change. Since these earlier studies, the characterisation of PrP^{Sc} molecular types has evolved and now sporadic CJD is classified into six phenotypic subgroups, by PrP molecular type and the polymorphism for methionine and valine at codon 129[27&28]. 70% of subjects showed the classic CJD phenotype (short illness duration, typical EEG and classical pathology), with PrPSc type 1 and at least one methionine allele at

codon 129 i.e. MM1 or MV1. However, 5 other subtypes were recognised with younger onset on average, a prolonged disease course, and an absence of EEG features. These are more difficult to diagnose and may be more difficult to distinguish from vCJD cases clinically. The presence or absence of psychiatric features or insomnia, for example, may aid in the distinction as in VV1 and MM2-C cases, insomnia, sensory symptoms and psychiatric features are not a feature. Psychiatric features and insomnia are characteristic of MM2-T subgroup, which is indistinct from FFI and to a lesser extent of MV2 and VV2 subgroups. The following table gives a summary of the Parchi classification. This was designed following the examination of a series of 300 patients.

Table 19: Summary of classification of sporadic CJD based on molecular and phenotypic analysis of 300 subjects; Parchi et al, 1999[27]

sCJD clinical group	MM1	MV1	VV1	MM2-C	MM2-T	MV2	VV2
codon 129	MM	MV	VV	MM	MM	MV	VV
PrP^{Sc} type	1	1	1	2-C	2-T	2	2
Clinical features	Rapidly progressive dementia, early, prominent myoclonus. Visual impairment or unilateral signs at onset in 40%	Rapidly progressive dementia, early, prominent myoclonus. Visual impairment or unilateral signs at onset in 40%	Progressive dementia	Progressive dementia	Insomnia and psychomotor hyperactivity in most cases in addition to ataxia and cognitive impairment	Ataxia, progressive dementia, long duration of illness (>2 years) in some cases	Ataxia at onset, late dementia
Sensory (% cases with signs or symptoms)	7	25	0	0	0	7	15
Psychiatric (% cases with signs or symptoms)	34	12	0	0	67	44	21
Insomnia (% cases with signs or symptoms)	8	0	0	0	67	15	15
EEG	typical*	typical	no typical EEG	no typical EEG	no typical EEG	no typical EEG	no typical EEG in most cases

Source: Parchi et al, Ann Neurol 1999; 46:224-233. SCJD = sporadic CJD *Typical = typical periodic sharp wave complexes

The psychiatric features of vCJD have been documented. Two of the original three reported cases presented with early psychiatric features with referral to psychiatric services[1-3]. In a review of the clinical characteristics of the first 14 cases it was noted that 9/14 had psychiatric symptoms at the disease onset, all developing psychiatric features early in the illness. 13/14 were referred to psychiatric services with a diagnosis of depression or depression secondary to an organic cause made[4].

Nine out of fourteen had insomnia; most had excessive sleepiness in the day, early in the illness. In those with depression, all but one had early weight loss and anorexia. 7/14 had symptoms of depression prior to any cognitive impairment and 2/14 had one episode of suicide ideation. Most had drug therapy, three with transient improvement. 2/14 had first rank symptoms of schizophrenia. Importantly, 12/14 had unsustained delusions that occurred within a few months of illness onset and were fleeting, lasting hours or days at most. 8/14 had visual, and 5/14 had auditory hallucinations. However, it was noted that ultimately a diagnosis of CJD was made by the development of sensory or other neurological symptoms or signs.
Although these early features are characteristic of vCJD there is still marked variability of presentation. Of three cases reported in Leicester, each had behavioural change and personality change at the onset and two were diagnosed with depression, but none had sensory symptoms, delusions or hallucinations[6].

In the review of the first 35 cases of vCJD, 34 had early persistent psychiatric features, most commonly depression, anxiety and withdrawl[63]. Five had first rank symptoms. Twenty-five were seen by a psychiatrist early in the illness and were given treatment. A later retrospective case note review of the first one hundred cases

confirmed that 38% of the cases were initially referred to psychiatry services, with 63% seen by a psychiatrist at some time. The most common psychiatric symptoms were dysphoria, anergia, loss of interest, anxiety and withdrawl. A small proportion developed hallucinations and paranoid behaviour or delusions. The fleeting delusions noted in the early reviews were shown to be relatively rare compared to other symptoms[70].

The difficulty with diagnosing vCJD early lies with the insidious onset and presentation with symptoms that could be attributed to many other illnesses. As part of the study to detect under-ascertainment of vCJD in Wales[61], a steering committee decided which ICD-9 diagnoses could be compatible with a diagnosis of vCJD at any stage of the illness and which may therefore constitute the differential diagnosis in the early stages of the disease. These included, alcoholic psychoses, drug psychoses, transient organic psychotic conditions (including acute confusional and subacute confusional states), schizophrenic psychoses, affective psychoses, paranoid states, neurotic disorders (anxiety states, hysteria, phobic states, obsessive-compulsive disorders, neurotic depression, neurasthenia, depersonalisation syndrome and hypochondriasis), personality disorders, sexual deviations and disorders, alcohol dependence syndrome, drug dependence, acute reaction to stress, adjustment reaction, depressive disorder and disturbance of conduct. The differential diagnosis is therefore broad and it is important to realise that sharing the possibility of prion disease with a patient who may be suffering from depression or anxiety may have far reaching consequences.

One window of opportunity for reaching an early diagnosis lies in the mean of 6 months before clear-cut neurological signs occur. It was felt that if further features of the psychiatric presentation could be distinguished early, this might aid in the identification of those with a progressive neurodegenerative illness.

Aim of the neuropsychiatric examination of patients with suspected vCJD

This was to test the hypothesis that there would be early distinguishing features in the psychiatric presentation of vCJD, in particular, a characteristic profile of depressive symptoms. These symptoms should be readily determined by formally assessing and quantifying changes in thought content, mood, symptoms of anxiety and personality change. The presence of a characteristic psychiatric profile may distinguish cases with vCJD from those with other causes of depressive symptoms.

Methods

A behavioural assessment was completed with 20 out of the 21 families enrolled in the study (14 families where a case of vCJD was confirmed and six with alternate diagnoses. The family of one case with probable vCJD (V5), were unavailable for completion of the tests). A battery of five tests was used in the form of an interview with the carer. In all cases the patient was too unwell and cognitively impaired to contribute. Each carer was interviewed personally by RJC and additional information was obtained from relatives, friends and nursing staff caring for the patient. The patients' medical notes were examined.

Assessment tools

The following assessment tools were used:

1. MOUSEPAD: Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia[77]. This test is based on the Present Behavioural Examination, though it is shorter and places equal emphasis on psychiatric and behavioural features in people with dementia. It was chosen as a tool to assess the non-cognitive features of dementia. It gives the benefit of allowing the measurement of phenomena in the last month and since the onset of dementia, with separate ratings for severity and frequency. This was scored with the carer in each case, as the patient was too impaired to give sufficient information.

2. CORNELL scale for depression in dementia[78]. This scale and the Clinical Anxiety Scale (CAS) were used because the MOUSEPAD does not include any items for depression or anxiety. It is a rating scale for depression in dementia that relies on observed and informant based questions rather than reports from the patient. It is a 19-item scale, rated absent, mild, intermediate or severe and a score of > 8 implies the presence of significant depressive symptoms.

3. CLINICAL ANXIETY SCALE (CAS)[79]. The CAS is an interview based measure which is a shorter version of the Hamilton Anxiety Scale. The person is rated by a clinician, who gauges how anxious the subject has been feeling over the past two days, including the present day, using six areas. The clinician is guided by detailed criteria for scoring each area. The scores are graded in four ranges i.e. recovered or absent; mild, moderate and severe. Validity is based on that of the Hamilton Anxiety Scale.

4. MEMORY FUNCTIONING QUESTIONNAIRE (MFQ)[80]. This tool was used to detect memory complaints and it was hoped that information from this would

supplement that obtained from formal neuropsychology testing. The MFQ was designed to detect memory complaints in the elderly. This tests 64 items on 7 scales of memory, rating retrospective functioning, frequency of forgetting, frequency of forgetting when reading, remembering past events, seriousness of forgetting and mnemonics usage. This scale should be self rated and also completed with an informant. However, only the latter was possible and therefore only an idea of the functioning "in the eyes of the carer" was obtained.

5. IDDD[81]. Interview to determine deterioration in daily functioning in dementia. This was used to assess the ability to perform the activities of daily living. The questionnaire refers to 33 self care activities and scores each on a three point scale i.e. independent, needing prompting and dependent, referring to behaviour in the last month compared to their normal level of function.

6. STANDARDISED ASSESSMENT OF PERSONALITY (SAP)[82]. The SAP was used to classify the subjects' premorbid personality. It was expected that our control group would consist of many young people without vCJD, but with some psychiatric features in common with the early stages of vCJD. It was important to establish whether people with certain personality traits experienced these symptoms. This test did not assess personality change as a result of illness. The assessment was based on an interview with an informant to classify the patients' premorbid personality in clinical terms. The result is classification into one of eleven types: self-conscious, schizoid, paranoid, cyclothymic, obsessional, anxious, neurasthenic, explosive, sociopathic, hysterical or "normal". Two grades of severity are noted i.e. the presence of a trait and a severer level if the subject is handicapped in day to day life by the personality trait. The test is performed in three stages. Firstly, the relationship and length of acquaintance with the patient is established. An

exploratory section follows this, when a description of personality is requested. Seven standard questions are used if the response is not helpful. Key descriptive words e.g. houseproud, shy etc are circled on a list in the proforma. Finally, more detailed questions relating to an emerging personality trait are explored.

Definitions of psychiatric terms

Delusions

Delusions were defined according to Goldberg (1987) and Cummings (1985) as "mistaken beliefs which are held with conviction, which are not shared by others of the same cultural or social background and intellect and which persist despite evidence to the contrary"[83&84]. The presence of delusions was based on evidence given by the carer, through information given in the MOUSEPAD. Delusions were measured a) if they had occurred at any time since the onset of the illness and b) in the last month. They were divided into simple delusions (Cummings, 1985) e.g. of theft or suspicion, or complex. The presence of persecutory ideation was also noted where ideas of persecution were not held with delusional intensity. The presence of delusions was also rated as 0, absent, 1 mild (less than once per week), 2 moderate (< 4 out of 7 days per week, and 3, severe (greater than four times per week).

Disorders of perception: Hallucinations and misidentifications.

Hallucinations were defined as "perceptions that are not based on external stimuli". The presence of visual hallucinations was noted if the subject reported seeing someone or something without an external stimulus or if they had been observed

interacting with such a non-existent person or object. Misidentifications were defined using the classification of Rubin (1988) with additional categories[85&87]:

a) people in the house – a belief based on misrecognition, that others are living in the house

b) misidentification of mirror image whereby the subject has indicated an inability to recognise the subjects own reflection in the mirror or "someone else is in the mirror"

c) misidentification of TV images – such that the patient is talking to the TV or is fearful that an event on screen is taking place in the room

d) misidentification of people – mistaking a relative or friend for another e.g. spouse for a daughter or brother.

Details were taken from information given by the carer during the MOUSEPAD test.

Behavioural disorders

Details of wandering, following the carer about the house, eating behaviour (increased amount or eating more quickly) sleep patterns, sexual behaviour, aggression (verbal and physical) and emotional lability were all taken during the MOUSEPAD. The presence of symptom, the stage of the illness it occurred at and its severity were scored for each case from details given by the carer.

Mood disorders

The presence of symptoms of depression was recorded as positive responses to items on the Cornell Scale for depression performed with the carer. The carer was therefore asked to judge the subjects inner feelings e.g. depressed mood, anxiety, feelings of

hopelessness and vegetative symptoms e.g. sleep disturbance, weight loss and diurnal variation in symptoms.

Personality

This describes acceptable attributes that have been present since adolescence, are stable overtime despite fluctuations in mental state, which are manifest in different environments and which are recognisable to friends and acquaintances[82].

Results

The time of disease onset is taken as the time when the family, sometimes with hindsight, felt that there had been a change in personality or behaviour, if this preceded other clinical symptoms. The mean time to seeking medical attention in all confirmed cases of vCJD was five months (range 0-18 months) and all cases, except two visited their general practitioner in the first instance. The time taken to seek medical attention in the comparative group, with alternative diagnoses ranged from 1-60 months (data not available for one case). Of the two cases presenting within one month of symptom onset, one presented with a psychotic episode and so made immediate contact with medical services and the other had a rapidly progressive course, later consistent with sporadic CJD (tables 20 and 21).

Table 20: Milestones in diagnosis (Variant CJD)

	Time to medical attention (months)	Who did patient first see?	Time to neurology opinion (months)	Time to psychiatric opinion (months)	Time to final diagnosis (months)
V1	3	GP	9	8	11
V2	0	GP	12	NA	14
V3	2	GP	13	9	13
V4	9	GP	12	10	13
V5	11	GP	16	NA	16
V6	18	GP	20	21	25
V7	na	na	11	NA	12
V8	5	GP	8	NA	13
V9	3	GP	5	NA	11
V10	3	GP	8	NA	11
V11	8	GP	8	NA	15
V13	0-4	GP	5	NA	15
V14	5	na	5	NA	18
V15	0	GP	7	NA	9
V16	7	GP	20	14	20

GP – General Practitioner; NA – Not applicable; na – not available

Table 21: Milestones in diagnosis (other diagnoses)

	Time to medical attention (months)	Who did patient first see?	Time to neurology opinion (months)	Time to psychiatric opinion (months	Time to final diagnosis (months)
O1	60	GP	72	NA	84
O2	na	GP	5	NA	8
O4	7	GP	23	12	23
O5	1	na	7(UK)	NA	7
O6	6	Physician	9	NA	21
O7	1	GP	NK	1	undiagnosed

GP – General Practitioner; NA – Not applicable; na- not available

Personality change or a change in behaviour was present at the onset of disease in 11 out of 15 cases. Seven out of 15 cases were diagnosed by their GP with depression and at least 7 out of 15 were treated with antidepressant medication (In many instances there were conflicting reports from relatives as to whether there was a response to antidepressant therapy. As insufficient supportive evidence was available, a figure for the response rate has not been included). Five out of 15 cases were referred to a psychiatrist with appointments on average 12 months from disease onset (range 8-21 months). All cases were referred to neurologists during the disease course at mean time 11 months from disease onset (range 5-20 months). The time to reach a diagnosis (taken as the time to the availability of the result of a tonsil biopsy) ranged from 9-25 months; mean 14 months from disease onset (table 22).

Table 22: Psychiatric Milestones (Variant CJD)

	Diagnosed with depression	Who made diagnosis?	Treated with antidepressants?	Referred to a psychiatrist?	Any other psychiatric diagnosis?
V1	Y	GP	Y	Y	N
V2	N	NA	NA	N	N
V3	Y	GP	Y	Y	N
V4	Y	GP	Y	Y	N
V5	N	NA	NA	N	N
V6	Y	NK	Y	Y	Y
V7	N	NA	NA	N	N
V8	N	NA	NA	N	N
V9	Y	GP	NK	N	N
V10	Y	GP	Y	N	N
V11	N	NA	NA	N	N
V13	Y	GP	Y	N	N
V14	N	NA	NA	N	N
V15	N	NA	NA	N	N
V16	Y	GP	Y	Y	N

GP – General Practitioner; NA – Not available; NK – Not known

In the comparative group with alternative diagnoses, there was early personality or behavioural change in all cases. Two cases were diagnosed with depression and 2 were definitely treated with antidepressant therapy. Both of these cases were later confirmed to have familial CJD (table 23).

Table 23: Psychiatric Milestones (Other Diagnoses)

	Diagnosed with depression	Who made diagnosis?	Treated with antidepressants?	Referred to a psychiatrist?	Any other psychiatric diagnosis?
O1	Y	GP	Y	Y	N
O2	N	NA	NA	N	N
O4	Y	Psychiatrist	Y	NA	N
O5	N	NA	NA	N	N
O6	N	NA	NA	N	N
O7	N	NA	NA	Y	Y

GP – General Practitioner; NA – Not available

Disorders of thought content: Delusions and persecutory ideation

Table 24 outlines the prevalence of disorders of thought in the 14 cases with definite or probable vCJD. Eight out of these 14 cases had experienced disorders of thought content since the onset of the illness, 5 female, 3 male, mean 5 months from disease onset (range 1-20 months). All were simple delusions. The most common was of theft (36%), of mild to moderate severity, on average occurring 12 months into the

illness (earliest 5 months from illness onset). Four out of 14 cases expressed delusions of suspicion, three of which experienced severe delusions of being watched. Other delusions were of abandonment (3/14 cases), the house not their own (2/14 cases) and someone else in the house (2/14 cases). The fears of abandonment were severe in two cases and in one case occurred early in the disease (within one month). This was notably the case with a young age at onset (<16 years of age).

In the comparative group with alternative diagnoses, four out of the six cases tested had disorders of thought, at mean time 22 months from illness onset (range 2-72 months). The most common was of suspicion (50% of cases) i.e. of poisoning, being followed and that their spouse was having an affair. One case (O7) presented with florid delusions on two occasions, linked to drug ingestion.

Table 24: Disorders of Thought; vCJD group

	Number of cases (%)	Severity of symptoms	Months from illness onset mean (range)
Any	8 (57)	1-3	
Theft	5 (36)	1-2	12 (5-25)
Suspicion	4 (29)	1-3	10 (6-20)
Abandonment	3 (21)	3	12 (1-25)
House not own home	2 (14)	nk	6 (5-7)
Someone else in house	2 (14)	1-3	16

nk – not known

Disorders of perception: Hallucinations and misidentifications

Only one case of the 14 cases with definite or probable vCJD had experienced auditory hallucinations and two, visual hallucinations, by the time of referral. The first case described two statues of dogs on the mantelpiece talking to each other. The first with visual hallucinations would hold things that were not there and try to give them to her parents. The second complained of seeing people outside the window. Misidentifications of any type occurred in 5/14 cases. The most common was of misinterpreting TV images as real events in four cases with definite or probable vCJD (in one case just one such episode was reported), on average eight months from illness onset, 2 with mild and one with severe symptoms (table 25).

In the comparative group, case O7 had marked auditory hallucinations during psychotic episodes. Case O5, developed disturbing, visual hallucinations 8-9 months from the onset of his illness. These were of mermaids, snakes on his bed and fire, which were very distressing to the patient. Case O1, who was later diagnosed with familial CJD, spent time conversing with herself in the mirror about six to seven years into her illness. Case O7 accused his sister and aunt of not being who they claimed to be and misinterpreted TV images as real events.

Table 25: Disorders of Perception; vCJD group

MISIDENTIFICATIONS	**Number of cases (%)**	**Severity of symptoms**	**Months from illness onset (range)**
Any	5 (36)	1-3	8 (5-10)
Mirror Image	0 (0)	nk	nk
People	3 (21)	1-2	8 (5-10)
Television	4 (29)	1-3	8 (7-10)

Behavioural change

Behavioural disturbance as distinguished from responses from the MOUSEPAD showed that all 14 cases with definite or probable vCJD had some behavioural change anywhere from one to 23 months from illness onset (table 26). The most common features were, aggression, sleep disturbance and emotional lability. Aggression was seen in 79% of cases, on average appearing 7 months into the illness (range 1-15). Eleven out of 14 expressed verbal and 3/14 physical aggression. Sleep problems were seen in 11/14 cases, on average 9 months into the illness. Nine out of 14 were restless at night (on average 9 months from illness onset) and 9/14 dosed in the day (mean 8 months from illness onset). Seventy-one percent showed emotional lability 8 months on average into the illness (1-19 months range); four of fourteen did so by inappropriate laughing and 9/14 by inappropriate crying.

Six out of 14 cases with definite or probable vCJD had a tendency to wander or follow on average six months into the illness but this may have been curtailed by the onset of balance and therefore walking problems. Changes in eating and sexual behaviour were much less frequent.

In the comparative group, all cases showed some behavioural change, 2 months to 6 years from illness onset. All cases had become aggressive (3 both verbally and physically, 4/6 physically aggressive). All cases also had sleep disturbance. Four out of six cases had become more emotionally labile.

Table 26: Behavioural Features; vCJD group (14 cases with definite or probable vCJD)

	Number of cases (%)	Severity of symptoms	Months from illness onset mean (range)
Any	14 (100)	1-3	(1-23)
Aggression - any	11 (79)	1-3	7 (1-10)
Aggression - verbal	11 (79)	3	7 (1-15)
Aggression - physical	3 (21)	1-3	6 (4-10)
Wandering or following	6 (43)	1-3	7 (1-13)
Eating more/more quickly	2 (14)	2	8 (6-10)
Sweet tooth	4 (29)	2	6 (5-8)
Sleep disturbance - any	11 (79)	1-3	9 (1-23)
Restless/ wakeful	9 (64)	1-3	8 (1-23)
Sleeping in day	9 (64)	1-3	8 (6-15)
Sexual disinhibition	2 (14)	1	8 (6-10)
Emotional lability - any	10 (71)	1-3	8 (1-19)
Emotional lability - laugh	4 (29)	1-3	10 (1-19)
Emotional lability - cry	9 (64)	1-3	8 (1-19)

Mood disturbances

In 10 out of the 14 cases with definite or probable vCJD, the families reported that they felt that the subject had symptoms that could be attributed to depression early in the illness. Only one case had a past medical history of depression. The Cornell scale for depression should be scored for symptoms experienced in the last week. The average score for the Cornell was 15.6 (range 5-31) with 11/14 (79%) cases scoring greater than or equal to 8, indicating evidence of severe depression. Breakdown of the Cornell scores shows that symptoms covered all aspects i.e. mood related, behavioural disturbance, physical signs and cyclic aspects of depression, though ideational disturbance was less common. Only 5/14 cases demonstrated suicidal ideation at any point in the illness. Of particular interest, 12/14 cases showed evidence of anxiety, 13/14 irritability and 9/14 showed agitation (table 27).

In the comparative group, 3 of the cases were considered to have symptoms of depression at some point in their illness. Scores on the Cornell scale for depression ranged from 11 to 24. Four out of five cases tested with the Cornell in this group, showed symptoms of anxiety, 4/5 had symptoms of agitation, and all (5/5) were irritable.

Table 27: Mood Disturbance; vCJD group

CORNELL	**Number of cases (%)**	**Mean score (range)**
Mood related signs	14 (100)	4.5 (1-8)
Behavioural disturbance	12 (86)	4.0 (0-7)
Physical signs	13 (93)	3.5 (1-6)
Cyclical functions	11 (79)	3.8 (1-8)
Ideational disturbance	7 (50)	3.1 (1-7)
Overall mean score (range of scores)		15.6 (2-31)

Activities of daily living

In these reports by the caregivers, all of the 14 patients with definite or probable vCJD were more dependent in daily activities than before the onset of the illness. Scores on the IDDD, ranged from 49-139, mean 96, indicating moderate to severe disability. The mean score for complex activities was far greater than that for self care activities, but this was due to a much greater use of score 9 i.e. caregiver not able to judge the initiative of performance, mainly in this patient group because of the movement or balance disorder prohibiting this activity or action.

Most help was needed with actually performing self-care activities such as getting washed, dressed, making food and eating it. Less assistance was needed with being reminded to eat or use the toilet. The patient needed more help with complex tasks such as expressing themselves and understanding what people said. Scores were high

for paying for items in shops, help with payment, switching off the cooker etc as these were scored as 9 by the carer as the patient no longer did the shopping or cooking for example.

In the comparative group, scores on the IDDD ranged from 47 – 194, indicating that these cases were also very dependent on carers for the activities of daily living.

The assessment of premorbid personality traits

On examination using the SAP, all of the cases were classified by informants as having a "normal" premorbid personality.

Discussion

The occurrence of psychiatric disorders, especially depression has been well documented in CJD. Behavioural disturbance, including a change in personality i.e. self-neglect, apathy, or irritability, depression, paranoia, a schizophrenia-like illness, euphoria and hypersexuality are documented. Psychiatric problems are among the more difficult problems in a differential diagnosis and often in CJD many alternative psychiatric diagnoses may be considered before the true situation becomes apparent[90]. This is further complicated by the additional diagnosis of depressive pseudodementia. Depression is found in over 30% of cases with CJD and it is not infrequent for a diagnosis of depressive pseudodementia to precede one of CJD[91]. This is thought to be in part due to some cases having a long clinical course before neurological signs occur, the associated locomotor or visual symptoms which are liable to be taken as conversion symptoms, that the disease may seem to be precipitated by life events and

that periods of stability can occur. Other "hysterical" presentations of CJD are documented. One case was initially described as a hysterical aphonia with anxiety and irritability (with a transient hallucinatory psychosis), prior to a diagnosis of CJD[92]. Other presentations include for example features of an obsessive-compulsive disorder with anorexia nervosa and mirthless laughter[93&94].

The presentation of patients with vCJD is characterised by the onset of symptoms of depression with associated fleeting delusions, personality and behavioural change. However, the presentation is not uniform and we are yet to confirm the disease phenotype in different age ranges and within different genetic subgroups of the population. The aim of this study was to characterise the early psychiatric features of the illness in more detail.

From an initial review of the notes from the GP and psychiatrists and from a retrospective view with the families, all cases would fulfil the criteria for major depression at some stage in the illness (except for the incompatability of these criteria when considering depression with an organic cause). All cases scored highly on the Cornell scale for depression indicating a high level of depression in the patient group at the later stage of the illness. These results need to be interpreted with caution as the test was scored with a carer and not the patient in the first instance. The carers all expressed the difficulty in limiting their answers to their experience with the patient over the last week and tended to score the case on the evidence of depressive symptoms over the duration of the illness. Also, the sleep disturbance, agitation and cognitive deficit, including a lack of concentration and lack of interest, features of the dementia syndrome, are common to those of depression and so a high score may not

be a true indicator of the level of depression in this patient group. All of the patients did lack insight to a certain degree. In the study of AD patients[86-89] it was noted that patients with severe cognitive impairment had fewer complaints of depression but did not differ in terms of observation of depression (by interviewer or relative) or past medical history of depression. Whilst no particular profile of symptoms of depression predominated, there were additional symptoms experienced by all 14 subjects with definite or probable vCJD, which were persistent and would not be considered as compatible with a single diagnosis of depression, even early in the illness. 14/14 had mood or behavioural change, and of these many had additional features: 6/14 had an unsteady gait, 9/14 had sensory limb symptoms of pain or paraesthesiae, 6/14 cognitive problems, 2/14 had visual problems, one had difficulty passing urine and one case, urinary incontinence.

Other psychiatric features of vCJD include delusions, fleeting and complex in vCJD. In the AD group[86] a significant proportion of subjects suffered from associated delusions or persecutory ideas. Theft and suspicion were the most common, the former more common in men. Cognitive function bore no relationship to the presence of symptoms. In this study 8 out of 14 cases with definite or probable vCJD were found to have disorders of thought content, mostly simple delusions, again theft and suspicion the most common.

Disorders of perception occur commonly in AD. Misrecognition and misidentification occurred in 30% of Burns' sample[87]. The most common in men are the misidentification of people and thinking that people are in the house, more commonly in younger patients. In the same study hallucinations were found to be

associated with a more rapid decline in AD. In CJD, 10-15% of cases have visual hallucinations, but these were often felt to represent misperceptions. However, it is thought in vCJD, that they are most likely to be true hallucinations. In this study group, there were only three cases with definite or probable vCJD who experienced hallucinations (two with visual and one auditory hallucinations). Misidentifications were more commonly encountered (36% of cases), the most common, misidentifiying TV images as real events.

Behavioural problems in patients with AD are common, with 20% of Burns' group aggressive, 19% wandering, 10% binge eating, 6% hyperorality, 48% with urinary incontinence, 7% sensory disturbance, all greater with increased severity of dementia.

Behavioural problems were also seen in all of the cases with definite or probable vCJD in our study group. The most common was aggression (11/14 verbal, 3/14 physical), sleep problems i.e. restless at night or dosing in the day. 71% of our cases showed emotional lability, most commonly of inappropriate laughing. Changes in eating behaviour or sexual disinhibition were far less common.

The overall severity of dementia cannot be assessed without looking at cognitive impairment, disability in daily life and behavioural disturbance. Often it is assumed that impaired functioning in daily life can be estimated from the cognitive impairment assessed during formal psychology testing. However, this is tested in an unfamiliar situation. The IDDD was devised to look at performance during daily living activities that are familiar. In our study, scores obtained from the IDDD reveal a high level of dependence of the person on the caregiver covering a general spread of activities of

daily living, cases tending to score more highly on needing assistance with tasks rather than needing reminding to carry them out.

Premorbid personality is an important factor in both the diagnosis and prognosis of psychiatric illness. It is interesting to establish that all cases tested, whatever the final diagnosis, were classified as having "normal" premorbid personalities. At the end of the study we did not have any young people in the control group with an abnormal personality trait, with psychiatric symptoms suggestive of vCJD.

The comparison group had a range of alternative diagnoses i.e. 2 with sporadic CJD, 2 with familial CJD, one with Lafora Body disease and one case with a psychotic disorder. The results of the behavioural study in these cases only illustrate that the constellation of disorders of thought, perception and mood can occur in a variety of rare illness, seen in young people. However, the cases are ultimately distinguished from those with vCJD by their lack of progression to further neurological signs compatible with the diagnosis.

Conclusion

The hypothesis that it would be possible to elicit distinguishing features in the psychiatric presentation of patients with vCJD was simply not realised. It was possible to highlight the additional sensory, movement and cognitive symptoms experienced by patients that would not be compatible with a single diagnosis of depression. It was also possible to give details regarding the proportions of patients with definite or probable vCJD who experienced disorders of thought, perception and

behavioural problems. Novel information was collected regarding the range and type of disorders documented.

STUDY IB: A STUDY OF THE COGNITIVE FEATURES OF CJD

Introduction

Dementia characterizes all but a small group of patients with sporadic CJD. MM1 and MV1 patients can lapse into coma abruptly after showing neurological signs at the onset without the appearance of dementia[27]. Cognitive impairment is invariably present at onset in VV1 and MM2-C subtypes but occurs later in the VV2 subtype (in this group only 27% of cases had cognitive impairment at the onset of the illness). The MM2-T subgroup is indistinguishable from cases previously described as having the thalamic form of CJD and indeed fatal familial insomnia (FFI). The behavioural and cognitive features of FFI are well described[95]. FFI is characterized by a picture of cognitive decline, with fluctuations in attention and vigilance levels, associated with disturbances of memory and temporal organization and may also occur on a sporadic basis[96].

Dementia is a variable feature of familial prion disease. Kindreds have been described with phenotypes of classical CJD and Gerstmann-Straussler Scheinker (GSS) disease but also with a range of neurodegenerative syndromes. There is often marked phenotypic variability even within one family[31]. Progressive dementia is seen to a variable extent and at a variable time in the illness with different mutations.

In some forms of iatrogenic prion disease such as those where the infectious material is inoculated centrally in the nervous system, for example following corneal transplantation or the use of inadequately sterilized neurosurgical or electrophysiological instruments[32-34], the ensuing illness resembles classical sporadic

CJD with a rapid dementia syndrome. Other iatrogenic forms for example, following the peripheral administration of human cadaveric - pituitary derived growth hormone, have a cerebellar onset and dementia occurs later in the illness and as a minor component[36&37]. However, in this group of young cases, mild cognitive impairment (in the form of a significant decline in general intelligence) is detectable at an early stage of the illness (mean 4.5 months from illness onset).[97]

There is experience of the oral inoculation of humans with prions in the study of Kuru, a prion disease thought to have been spread by cannibalism in a tribe in Papua New Guinea. In this disease dementia is often absent, although in the terminal stages, it has been reported that the patients faculties are often obtunded[98].

Pronounced cognitive decline appears to be a feature of vCJD. This may aid in its differential diagnosis from other forms of prion diseases and other neuropsychiatric conditions. However, a neuropsychology profile providing the distinguishing features of vCJD and the stage in the illness at which it occurs, has yet to be established; only qualitative and anecdotal accounts of cognitive decline have been reported to date.

Two of the first three published cases of vCJD presented with symptoms of forgetfulness and intermittent confusion from the onset of the illness. Bateman et al, describe an 18 year old male, who complained he had "gone nutty"[2]. He complained of a reduction in short term memory and was found to be disorientated in time, place and person. Tabrizi et al, describe a 28-year-old female presenting with increasing forgetfulness and confusion, who on examination three months into the illness was found to have a reduced short-term memory[3]. Progressive deterioration in cognition

was reported in all three cases. A further report of the first 14 cases of vCJD revealed a rapid progression to global cognitive impairment in most cases[5]. Fluctuations in individuals' performance over hours or days were noted. Three cases were reported from Leicestershire with more atypical clinical phenotypes and significant cognitive impairment[6]. In particular, patient 1 showed impairments of memory, verbal fluency, spatial judgement and a decline in language functions; patient 2 showed severe behavioural change, characterised by emotional lability and aggressiveness and patient 3, memory impairment and personality change.

In a review of the first 35 cases of vCJD, 6 out of 35 had early symptomatic cognitive impairment and all progressed to a dementia syndrome later in the illness[63]. In ten patients the neuropsychology assessment occurred after the development of neurological symptoms. Cognitive impairment was reported in all cases. In the retrospective case note review of the first one hundred cases, it was suggested that often the possibility of the diagnosis of only realised with the onset of cognitive impairment. From this analysis it was noted that cognitive decline developed a median 4-7.5 months from illness onset and included poor memory, concentration, disorientation or even overt confusion. In a very small proportion these features were present at the earliest stage[70].

Detailed quantitative neuropsychology data have been reported in only one previous study. This single case study reports a detailed profile showing intellectual decline, severe memory impairment and executive dysfunction[99]. Some longitudinal data are included showing progressive decline over a four-month period.

In this section of the study, the detailed neuropsychology profiles of 12 cases are described. The data are compared with cross sectional data obtained from patients with histologically confirmed sporadic CJD and cases with familial CJD with confirmed mutations in the prion protein gene.

Aim

This was to test the hypothesis that there is a characteristic neuropsychology profile of patients with vCJD and that this would be distinct from the profiles of cases with sporadic and familial prion diseases in the control group.

Methods

In this study, formal neuropsychology agreed to by 10 out of the 15 cases enrolled with definite or probable vCJD. Data from two cases of definite vCJD seen prior to the study were added to this patient group. The control group was formed from 10 patients with sporadic disease and 18 cases with familial CJD all seen at the NHNN and the Prion Unit, St. Mary's Hospital, London during the study period. All of the familial cases had a confirmed mutation in the PRNP gene and symptoms attributable to the disease. There was histological confirmation of disease for all ten sporadic cases, 8 from post mortem examination and two from brain biopsy. Case O4 with familial disease was included in the familial prion group and O5 was included in the sporadic prion disease group. The mean age and sex distribution of these study groups are given in table 28. The clinical details are given in table 29.

Table 28: Neuropsychology assessment: Mean age and sex distribution of the cases

	Variant CJD			Sporadic CJD			Familial CJD		
	N	Mean age (years)	SD	N	Mean age (years)	SD	N	Mean age (years)	SD
Males	5	28	7.3	8	55	8.7	12	42	10.0
Females	7	23	4.6	2	56	6.0	6	40	4.2
Total	12	25	6.3	10	55	8.7	18	42	9.0

The following neuropsychology test battery was used:

General Intelligence	Wechsler Adult Intelligence Scale Revised, WAIS-R[100] Coloured Progressive Matrices[101]
Verbal and Visual Memory	Recognition Memory Test, RMT[102]
Nominal Skills	Graded Difficulty Naming Test, GNT[103] Oldfield Picture Naming Test[104]
Literacy Skills	National Adult Reading Test, NART[105]
Visual Perception and Visuospatial Function	Fragmented Letters Object Decision Dot Counting Cube Analysis Position Discrimination[106]
Executive Function	Wisconsin Card Sorting Test, WCST[107] Weigl Sorting Test[108]

The WAIS-R was used to calculate an intelligence quotient (IQ) for each person i.e. a number used to express the person's performance in intelligence tests and represents the ratio of the subject's score to the statistical norm for a population group (IQ=100 being average). A verbal IQ (VIQ), performance IQ (PIQ) and a full IQ (FIQ) were calculated. The NART provided, not only a measure of reading skills, but also an estimate of the premorbid optimal level of functioning (reading IQ equivalent). Values for the full, verbal and performance IQ were predicted from the number of errors made on the NART. The intellectual functioning score was calculated from the difference between the NART expected IQ values and the observed IQ values. (A difference of 10 indicates mild intellectual decline, 11-20 moderate decline and greater than 20, severe intellectual decline). In individuals who presented with acquired dyslexia, education and occupational background were used to provide evidence of premorbid ability.

Test scores for memory, naming and perceptual function are difficult to interpret in isolation. Age specific conversion tables are available which allow the conversion of raw scores to percentile scores. Scores at or below the 5^{th} percentile indicate memory, naming or perceptual impairment. Performance on the Weigl sorting test was taken as impaired if the subject could reach only one or none of the two solutions.

Statistical Analysis

As the NART was not used as an estimate of premorbid intellectual function in some cases, it was not possible to apply a statistical method to compare the degree of intellectual decline between the three disease groups. However, the proportions of patients presenting with deficits in each of the five cognitive domains (verbal and

visual memory, naming, visuoperception and frontal executive function) were compared using Fisher's exact test. Fisher's exact test is a signicance test for two or more groups with different subjects but small samples. Data were analysed using STATA, release 6.0 (Stata Corperation, College Station, Texas). This programme can readily compute Fisher's exact test for larger tables (i.e. larger than the 2x2 tables for which the test was originally devised). The test was applied first to a 3x2 table as there were three comparisons being made e.g. the proportion of patients with verbal memory impairment in each group was compared between 1) variant versus sporadic; 2) variant versus familial and 3) sporadic versus familial. Where the p value is > 0.05 it implies that there is no evidence against the null hypothesis that all 3 proportions are equal. One p value in the 3x2 table was significant and so three different 2x2 Fisher's exact tests were then done relating to each of the 3 comparisons given above, to see where the difference lay.

Results

Comparing first, the vCJD with the sporadic and familial cases, it was noted that the patients with vCJD were significantly younger. There was a preponderance of males in the familial and sporadic groups. The mean duration of illness at the time of assessment was 12.4 months (range 9-25) in the variant group, 41.7 months (range 1-132) in the familial group and 7.7 months (range 1-15) in the sporadic group.

The clinical characteristics, imaging and EEG findings from this selection of patients can be compared using table 29.

Table 29: Clinical features of all cases undergoing neuropsychology assessment

	PRNP mutation	personality ch'ge/dep'sion	cognitive decline	sensory symptoms	chorea dystonia	myoclonus	ataxia	pyramidal	extrapyramidal	MR atrophy	MRI signal change	EEG p'dic complexes	EEG nonspec. abnormalities
V1	-	+	+	+	+	-	+	+	-	-	thalamus	-	+
V3	-	+	+	+	+	-	+	-	-	-	thalamus	-	+
V4	-	+	+	+	+	+	+	+	-	-	thalamus	-	+
V5	-	+	+	-	+	+	-	+	-	-	thalamus	-	+
V6	-	+	+	+	+	-	+	+	-	-	thalamus	-	+
V8	-	+	+	-	+	-	+	-	-	-	thalamus	-	+
V9	-	+	+	+	-	-	+	+	-	-	thalamus	-	+
V10	-	+	+	+	+	+	+	+	-	-	thalamus	-	+
V11	-	-	+	-	+	+	+	+	-	-	thalamus	-	-
V15	-	+	+	+	+	-	+	+	-	-	occipital white	-	+
V17	-	+	+	-	+	+	+	+	-	-	-	-	+
V18	-	+	+	-	-	-	-	+	-	-	-	-	+
F1	144	-	+	-	-	-	+	-	+	+	-	-	+
F2	P102L	+	+	na	na	-	+	+	-	-	-	-	+
F3	P102L	+	+	-	-	-	+	+	-	+	-	-	+
F4	A117V	-	+	-	-	+	+	+	+	+	-	nt	nt
F5	A117V	+	+	-	-	-	+	-	-	+	white matter	-	+
F6	E200K	+	+	-	-	+	+	+	-	+	-	-	+
F7	E200K	-	-	-	+	+	+	-	-	-	-	-	+
F8	144	+	+	na	na	-	+	-	+	+	-	-	+
F9(04)	novel*	+	+	+	-	-	+	+	-	-	mesial frontal	-	+
F10	144	+	+	na	na	+	+	-	-	+	-	-	+
F11	144	+	+	-	-	-	+	-	-	+	-	-	+
F12	144	-	+	-	-	+	+	-	+	+	-	-	+
F13	144	+	+	-	-	-	+	-	-	+	-	-	+
F14	144	+	+	-	-	-	-	-	-	+	-	-	+
F15	144	-	+	-	-	-	+	-	-	+	-	-	+
F16	144	+	+	-	-	+	+	-	+	+	-	na	na
F17	144	+	+	-	-	-	+	-	-	+	-	-	-
F18	144	-	+	-	-	-	-	-	-	+	-	-	+
S1	-	-	+	-	+	+	+	-	-	-	-	-	+
S2	-	+	+	-	+	-	-	+	+	na	na	na	na
S3	-	+	+	-	-	+	-	+	+	-	cortical	+	-
S4	-	-	+	-	-	-	-	-	-	+	-	-	+
S5	-	+	+	-	-	+	+	-	-	+	-	na	na
S6	-	-	+	-	-	-	+	-	+	-	-	-	+
S7(O5)	-	+	+	-	-	+	+	+	-	-	caudate,lentiform	-	+
S8	-	+	+	-	-	-	-	-	-	-	-	na	na
S9	-	+	+	+	+	+	-	+	+	-	-	+	-
S10	-	-	+	-	+	+	+	+	-	nt	nt	-	-

(nt = not tested; na = not available; *7 octarepeat insertion)

Ten patients could not be formally assessed, as they were unable to cope with the test demands (2 vCJD (V10 & V18), 6 sporadic and 2 familial cases). There were 8 patients with familial CJD who were assessed on more than one occasion (mean difference in months between assessments = 8.8 months); all were symptomatic at the initial assessment.

Table 30: Level of intellectual decline per patient group

	Variant CJD N=10	Sporadic CJD N=4	Familial CJD N=16
VIQ			
None	-	1	2
Mild Decline	1	-	1
Moderate Decline	2	-	3
Severe Decline	7	3	10
PIQ			
None	-	1	1
Mild Decline	-	-	-
Moderate decline	-	-	2
Severe Decline	10	3	13
FIQ			
None	-	1	1
Mild Decline	-	-	-
Moderate Decline	-	-	2
Severe Decline	10	3	13

The prevalence and degree of intellectual decline in the three patient groups are given in table 30. Significant intellectual impairment was seen in all three groups with the majority of cases presenting with severe decline in both the VIQ and PIQ. All of the vCJD cases had some degree of intellectual decline, severe in 70%. Two cases with familial disease were unimpaired.

Table 31 shows performance in each of the five cognitive domains. All of the vCJD cases had impairment of verbal and visual memory. This was true of all of the sporadic cases, with one exception. The patient with normal memory also had intact intellectual function. The prevalence of memory impairment was also high in the group with familial disease although there were cases with no impairment or selective modality specific memory impairment. Nominal skills were severely impaired in all patients with variant and sporadic CJD with only one exception in each group. This was in contrast to the group with familial disease where only a minority of patients had nominal impairment. This difference in the proportion of cases with nominal impairment, compared across the disease groups was statistically significant ($P = 0.006$). Three further pairwise comparisons of the proportions in each group was done to see where the difference lay. The proportion of patients with nominal impairment was statistically significantly different in the variant and familial groups ($P = 0.005$).

Fifty percent of the sporadic and familial cases had perceptual impairment. Strikingly, only 2 cases with vCJD (20%), both with severe, global cognitive decline had impaired perception. This difference in the proportion of cases in each disease group with perceptual impairment was not statistically significant ($P = 0.31$).

Frontal executive impairment was prominent in all three disease groups. All of the variant and sporadic cases tested showed frontal executive dysfunction. All except two of the familial cases also showed frontal executive impairment.

Table 31: Number of patients impaired in each cognitive domain per group (compared using Fisher's exact test)

	Variant CJD N=10	Sporadic CJD N=4	Familial CJD N=16	P value 3 way FE test
Verbal Memory†	10	3	11	0.13
Visual Memory†	10	3	13	0.32
Nominal skills†	9	3	5	**0.006**
Visual Perception†	2	2	8	0.31
Frontal	9*	3*	14	0.24

* Only 9 variant CJD patients tested

* Only 3 sporadic CJD patients tested

Standardised test performances converted to percentile scores or cut off points:

† ≤ 5th percentile indicating memory, naming and perceptual impairment

FE test = Fisher's exact test

Table 32: Three pairwise comparisons of the proportions of patients in each group with impaired nominal skills

NOMINAL SKILLS	Variant vs familial	Variant vs sporadic	Sporadic vs familial
P VALUE	**0.005**	0.505	0.255

Table 33 gives the longitudinal data for the eight cases with familial disease. All cases with intellectual decline at the first assessment showed evidence of progression at follow up. One individual, with no intellectual decline initially, remained

unchanged one year later. Similarly, all eight patients with impairment in one of the five domains at initial assessment also showed further progression on subsequent testing.

Table 33: Longitudinal data showing both severity of intellectual decline in familial cases (n=8), and the number of cases with impairment in each cognitive domain at baseline assessment

	1st Assessment	2nd Assessment
VIQ		
None	**2**	**1**
Mild Decline	**1**	**-**
Moderate Decline	**1**	**3**
Severe Decline	**4**	**4**
PIQ		
None	**1**	**1**
Mild Decline	**-**	**-**
Moderate Decline	**2**	**2**
Severe Decline	**5**	**5**
FIQ		
None	**1**	**1**
Mild Decline	**-**	**-**
Moderate Decline	**2**	**2**
Severe Decline	**5**	**5**
Cognitive domains		
Verbal Memory	**4**	**6**
Visual Memory	**6**	**7**
Nominal skills	**3**	**4**
Visual Perception	**4**	**4**
Frontal	**7**	**8**

Case O6, diagnosed with Lafora Body disease, underwent two assessments, 9 months apart. At the initial assessment, he was functioning in the borderline defective range on both the verbal and performance subscales of the WAIS-R, reflecting a marked

decline in his intellectual functions. He also had selective visual memory impairment and his nominal and frontal executive functions also impaired. This pattern was repeated at the follow up assessment, although there was some mild improvement in performance based on intellectual skills.

Post mortem histological examination of brain tissue was performed in five of the variant CJD cases in this part of the study. The disease had advanced significantly in all cases prior to death and so the pattern of histology would not directly reflect that at the time of testing. All five cases showed severe spongiform change, neuronal loss and astrogliosis in the basal ganglia and thalamus. These changes and florid plaques were seen to a lesser extent, throughout the cerebral cortex, most severely in the occipital cortex. Widespread prion protein deposition was demonstrated by immunohistochemistry. In three cases the cerebellum was noted to be severely affected (V1, 5 & 9). In one case where the hippocampus was studied, it was relatively spared (V11).

Discussion

These results indicate that moderate and severe intellectual decline is a characteristic of variant CJD. This is also true for sporadic CJD, but familial CJD patients are generally less severely impaired at early stages of an illness with a longer time course. The presence of cognitive impairment was high in all patient groups. Specifically, verbal and visual memory impairments and frontal executive dysfunction were pervasive in all patient groups. Nominal skills were similarly impaired in patients with variant and sporadic CJD. However, there was a statistically significant

difference in the proportion of cases with nominal impairment in the variant CJD group compared to the proportion in the familial CJD group.

In the vCJD group only a minority of patients presented with a perceptual impairment compared with half the patients in the sporadic and familial CJD groups, although the difference in the proportions affected in each group was not statistically significant. Clinically, the diseases differ mainly in their tempo and this is reflected in the cognitive profiles of the groups. This is also a limitation of the study in that it is difficult to match patients at comparable stages or severity of disease. The time course of familial CJD differs with each mutation type and the individual, but is usually longer than that of sporadic disease. The longitudinal data provide further evidence of this. Cases with classical sporadic CJD characteristically have a rapidly progressive dementia syndrome. Six out of ten of the sporadic cases in our study were already untestable at the time of referral to the National Hospital.

The patients in this study with vCJD showed rapid cognitive decline. At the time of assessment, (mean 12.4 months from illness onset), the majority had developed a profile of moderate to severe intellectual impairment, verbal and visual memory and nominal impairment and frontal executive dysfunction, with in many cases sparing of visuoperceptual functions. This was at a late stage in the illness when there were overt neurological signs. However, our experience of a further case, not part of this study, shows that this pattern may be seen as early as three months from illness onset.

Early cognitive decline may be related to the presence of some of the neuropsychiatric symptoms experienced by the cases. It is possible that perceptual disorders may

exacerbate hallucinations. Confusion and agitation may be confounded by a reduction in cognition and understanding. However, experience from the further case not part of the final study, who presented after only three months of symptoms, shows that cognitive decline can occur in the absence of psychiatric symptoms.

There has been one further case reported in detail in the literature, presenting at an early stage in the illness i.e. after only two months of symptoms[99]. The patient performed below average on tests of intellectual functioning (WAIS-R). He also showed impairment in verbal reasoning, naming and verbal fluency. However, he performed well on a face perception test. The authors noted the widespread distribution of spongiform change at autopsy, greatest in the caudate and putamen. There was also marked neuronal loss and astrogliosis in these nuclei, and in the dorsal and posterior thalamus and occipital cortex. Florid plaques were widely distributed. The authors suggest that primary subcortical damage (of the thalamus and neostriatum) with secondary frontal lobe dysfunction, may account for the pattern of generalised cognitive impairment.

The histological features of vCJD which distinguish it from the other forms of prion disease include spongiform change which is most pronounced in the basal ganglia, marked thalamic gliosis and pronounced PrP deposition in the occipital cortex and the molecular layer of the cerebellum (perineuronal and perivascular deposits)[73]. This pattern of histological change was demonstrated in our cases (post mortem histology was available for five cases with vCJD) with the basal ganglia and thalamus showing severe spongiform change, neuronal loss and astrogliosis. These changes and florid plaques were seen to a lesser extent throughout the cerebral cortex (most severely in

the occipital cortex). Widespread prion protein deposition was demonstrated by immunohistochemistry (including in the cerebellum).

From the available histology at the end stage of the disease, it is not possible to distinguish the origin of the cognitive decline that may primarily occur in cortical regions or through thalamic and basal ganglia degeneration. The dementia syndrome of fatal familial insomnia has been correlated with lesions in the anteroventral and medialdorsal thalamic nuclei and one of the characteristic features of variant CJD is the prominent reactive astrogliosis seen in the thalamus (pulvinar region). This is thought to account for the high signal seen on T2 and proton density MR images in the pulvinar region in these cases, called the pulvinar sign[109]. The pulvinar is a large region of the thalamus overlying the rostrolateral extent of the midbrain. This region is thought to serve one of the many functions involved in the visual system to generate visual perception. Computation of a scene by the visual system must be performed with speed and in great detail but with allowance for spatial constancy[110]. Some images in a scene are conspicuous and it is thought that one of the roles of the pulvinar is to indicate the salience of visual images and events. The retina projects to the contralateral pulvinar, which in turn has projections to the visual cortex and the association areas of the frontal and parietal cortices. It is interesting to note that in our group of eleven cases of vCJD, it was in fact the scores for visual perception, which appeared to be conserved until a later stage in the illness. However the tests performed were relatively simple and further examination of the patients' ability to determine the context of scenes and the relevance of images would be of value, as these skills have been shown to be lacking in a patient with pulvinar damage[110].

Further investigation should include examination of visuospatial relations and visual memory, as these are also determinants of image salience.

The study of the neuropsychology profiles of our cases confirms the occurrence of generalised intellectual decline in patients with vCJD and it further demonstrates that this may occur at an early stage in the illness course. There is a suggestion that although decline in cognitive function ultimately affects all domains, some components of visual perception may be spared by the pathological processes of vCJD. It may also be proposed that nominal function may be preserved in some cases with familial CJD.One case enrolled in the project, originally suspected of having possible vCJD (O6) was diagnosed with Lafora Body disease. Although neuropsychology testing at the initial presentation showed deficits in multiple cognitive domains, this case differed in that there was a failure of progression of these deficits at a rate seen in the other cases of vCJD.

Conclusion

It was not possible to prove the hypothesis that there is a distinct neuropsychology profile for early vCJD. However, investigation of cases at a moderately advanced stage of the disease has revealed some difference in the pattern of deficits seen in people with familial, sporadic and variant forms of prion disease.

STUDY IC: NEUROIMAGING IN CJD

Introduction

The neuroimaging features of the prion diseases are diverse. Progressive cerebral atrophy was first illustrated in a case of sporadic Creutzfeldt-Jakob disease (CJD) using CT. Imaging findings mirrored the severe brain atrophy seen at post-mortem[111]. The report of two sporadic and one familial case followed, in whom progressive cerebral atrophy was demonstrated using CT and MRI[112] and a study of three sporadic cases showed that atrophy was greatest where disease duration was longest[113]. This was in contrast to results from another study which found 80% of sporadic cases (12/15), to have normal CT images, irrespective of the time elapsed from clinical onset and three patients with the ataxic form of the disease did not have cerebellar atrophy detectable on CT or at post-mortem examination[114].

The original reports of signal change on MR images, describe hyperintensity on T2 images in sporadic CJD, in the basal ganglia and thalamus, corresponding to areas of pronounced spongiform change, gliosis and neuronal loss[115-117]. Subsequently, signal change has been shown in sporadic cases to be commonly observed, symmetrically in the caudate and putamina but also with varying frequency in many cerebral substructures such as globus pallidus, thalamus, occipital, cerebellar, and frontoparietal cortices[118&119]. These patterns may reflect alternative presentations of CJD, for example, increased T2 signal change in the occipital cortex has been reported in the Heidenhain variant of CJD (where cortical blindness is prominent) [120] and white matter degeneration has been illustrated in 2 separate reports of the "panencephalitic" variant of the disease[121&122]. Increases in T1 signal change in the

globus pallidus in one sporadic case, with the proposal that this may represent major PrP deposition, suggests that the range of findings visible using MR imaging in this group of diseases may be even wider[123].

Progression of disease has been illustrated using both changes in signal intensity and visualisation of atrophy using serial MR imaging. Reduction in signal intensity in the basal ganglia, the development of diffuse white matter signal changes and progressive cerebral atrophy have each been reported in sporadic CJD on serial imaging[124&125]. Hyperintensity of signal in the basal ganglia has also been reported in a sporadic case prior to the appearance of clinical and electrophysiological signs[126]. Similarly, a familial case is reported with increased cortical signal in the left frontal, parietal and temporal lobes. This extended into the right hemisphere and basal ganglia bilaterally on follow up images, and progressive frontal atrophy was also demonstrated[127].

The usefulness of MRI in the clinical diagnosis of CJD was recently assessed in a review of images from 162 cases referred to the German surveillance centre[128]. In 67% of sporadic cases, MRI showed bilateral symmetric hyperintense abnormalities in the caudate nucleus and putamina on T2 weighted and proton density images. Of 37 patients with serial imaging, 9 patients showed an increase in signal abnormality. Notably, in 6% of cases, MRI showed atrophy but no signal change, in 24% both atrophy and signal change were seen and 44% hyperintense alterations in signal but no atrophy were documented.

The interpretation of signal change as a means of monitoring disease progression is limited by the need to distinguish the changes in healthy tissue with age and the

degree of pathological change dependent on the stage of the illness in any individual. The combination of spongiform change (with accumulation of fluid in the vacuoles) and astrocytic gliosis are thought to account for the increase in signal on T2 and proton density images. The variation in T2 signal may be affected by the degree of iron deposition in the basal ganglia, which naturally increases with age and accounts for the usual hypointense appearance of the basal ganglia in the elderly[118].

It was noted during the course of CJD surveillance that high signal on dual echo, T2 or proton density images, had been reported bilaterally, in the pulvinar region (posterior thalamus). This was investigated further by the analysis of MR brain images from patients with vCJD and controls (i.e. those suspected to have vCJD but with alternative diagnoses and those known or suspected to have other forms of CJD) [109]. MR images were assessed by two independent neuroradiologists, blinded to clinical information. Scans with increased signal in the putamen and caudate head were diagnosed radiologically as sporadic CJD and those with predominantly increased signal in the pulvinar as vCJD and the degree of certainty graded. The sensitivity of radiological changes for diagnosing vCJD was 78%, with specificity 95%. To limit false positive results the authors proposed that only prominent changes should be deemed positive i.e. bilateral pulvinar signal intensity greater than all other basal ganglia on proton density weighted images, or greater than or equal to all other basal ganglia on T2 weighted images. This has been termed the pulvinar sign and the authors indicate that this may correlate with astrocytosis and neuronal loss, in this area, in these cases. (The authors estimate that the sensitivity and specificity of the pulvinar in the diagnosis of vCJD are 78% and 100% respectively). Measures of the degree of signal intensity in the posterior thalamus have been made[129]. It is known

that absolute signal intensities from MR images vary between scans performed on the same scanner and between images from different MR scanners. Further work has shown that there is wide variation in the signal intensities within a particular deep grey matter structure, the putamen [130]. Here there is also an anterior-posterior intensity gradient that may be quantified. A putamen to frontal white matter intensity ratio of 1.35 or greater was a useful test for distinguishing between sCJD and vCJD with 82% sensitivity and specificity. Relative signal intensities have been studied comparing signal intensity in the posterior thalamus with the caudate, putamen and frontal white matter on T2 and proton density images (from different MR scanners), in patients with vCJD[131]. The ratios were compared with those from a group of controls with sCJD and non-CJD dementia cases. A posterior thalamus to frontal white matter ratio on T2 scans gave the best discrimination between vCJD cases and controls using a threshold of 1.51 (sensitivity 100%, specificity 89%). Further studies are necessary to assess the possibility that the pulvinar sign may be present preclinically. More information is also needed about the prevalence of high signal in the normal population or those with other psychiatric or neurological conditions.

MR images were reviewed for all 21 cases referred with possible vCJD in the study. The presence of absence of the pulvinar sign was noted and an attempt was made to quantify the degree of signal change in the posterior thalamus in four cases. However, the image quality was insufficient for reliable results to be obtained.

Quantification of cerebral and cerebellar atrophy

MR imaging was reviewed in the first fourteen cases of vCJD reported by the CJD surveillance unit. Four of these cases had mild generalised atrophy and one was noted

to have slightly prominent ventricles[5]. Atrophy detected by structural imaging correlates with the spongiform change and accompanying neuronal loss characteristic of the prion diseases.

Quantification of cerebral atrophy may aid the distinction of CJD from the other degenerative dementias, such as AD, as these pathological processes preferentially affect different cerebral substructures. Rates of atrophy and patterns of tissue loss within cerebral substructures can be delineated from serially acquired registered volumetric MR images. This technique has been applied to the study of AD to quantify tissue loss and therefore show disease progression[132]. Progressive cerebral and cerebellar atrophy has also been demonstrated in one case of familial CJD[133]. In another study, measurements of cerebellar volume distinguished cases with vascular dementia from those with AD[134]. Although some of the pathological changes of AD are seen in the cerebellum and cerebellar atrophy was demonstrated in this study group, volume changes in the cerebellum were significantly less than those in vascular dementia.

Cerebellar symptoms and signs are often present in CJD and may be an early feature of variant and some familial and iatrogenic forms. The demonstration of cerebellar atrophy may therefore support a diagnosis of CJD. In this study, the volume of the cerebellum was assessed in patients with sporadic, familial and acquired forms of CJD compared to normal, age and sex matched controls. The quality of the images from the vCJD patients was poor due to movement artefact and so accurate quantificataion of cerebral and cerebellar volumes in this subgroup were not possible.

Aim:

To test the hypothesis that it is possible to demonstrate cerebellar atrophy in variant, iatrogenic and some familial and sporadic forms of CJD. The detection of cerebellar atrophy in early disease may lend support to a diagnosis of CJD.

The aim was also to test a second hypothesis that it is possible to quantify the annual rate of whole brain atrophy in patients with CJD.

Methods

Of the 23 patients enrolled in the study, only one case was able to tolerate further MR imaging (case O4 (F9)) to give an image of sufficient quality for volume measurements to be accurately performed. The study group was therefore expanded to include all patients seen in the Specialist Cognitive Disorders Clinic at the NHNN and the Prion Unit at St. Mary's Hospital, London, with a clinical diagnosis of CJD, and at least one adequate volumetric MR brain study. Only those with definite genetic or histological confirmation of CJD were included. MR images had to be of sufficient quality for accurate delineation of tissue/CSF boundaries. This excluded volumetric images from all cases of vCJD, which were too degraded by motion artefact for accurate measurements to be obtained. Fifteen patients were identified. The group comprised five sporadic and two human pituitary growth hormone derived cases, with pathological confirmation of the disease and 8 cases with familial disease with a mutation in the prion gene (see table 33). Each of the latter cases demonstrated clinical signs attributable to familial CJD at the time of scanning and post-mortem confirmation was available in three cases. Of the eight familial cases, 3 had a proline to leucine missense mutation at codon 102 and four cases had a 144 base

pair insertion[29&135]. One case had a novel mutation, (case O4, personal communication Professor J Collinge). The clinical details, age at onset and illness duration at the time of imaging, are summarised together in Table 33 for comparison (Cases F3, F9, F10, F15, F17, F18, S4, S5, and S9 also participated in the neuropsychology study). The age at onset is defined as the age at which symptoms of behavioural change, cognitive decline, visual problems or imbalance first became apparent, as estimated from reports given by the patient and corroborated by family members.

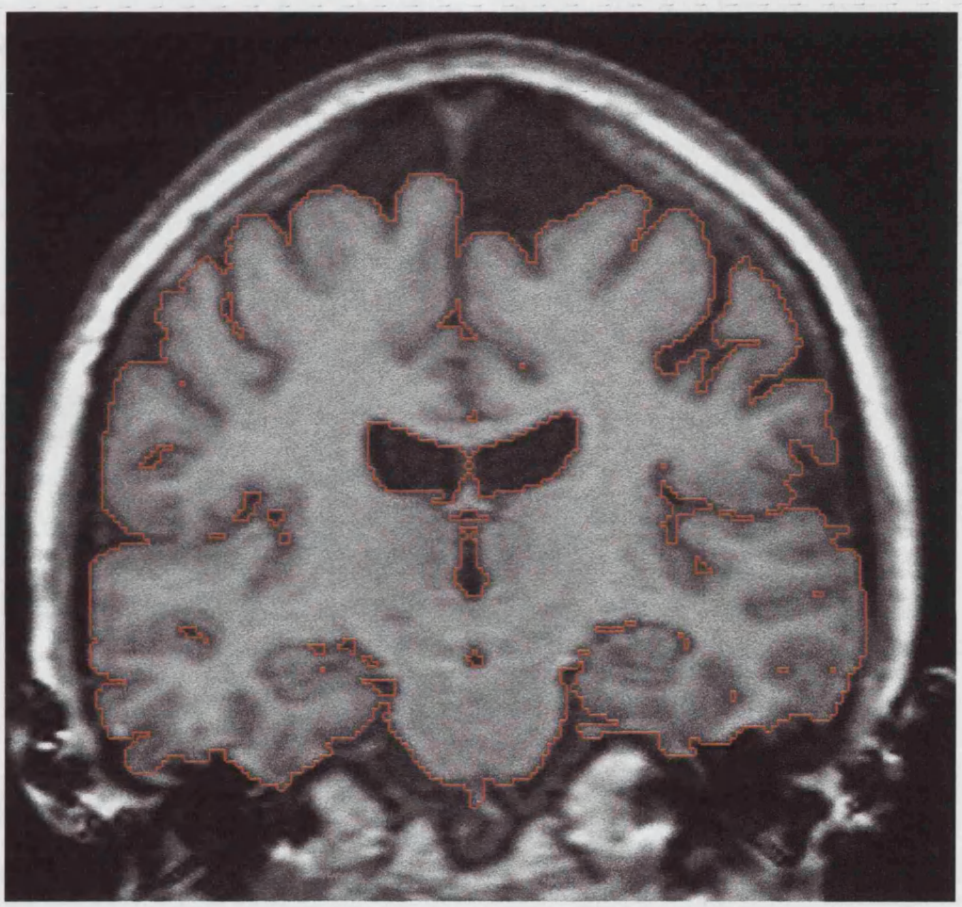
15 normal controls were selected from the database of the Cognitive Disorders Clinic at the National Hospital for Neurology and Neurosurgery. These were healthy spouses of patients and volunteers from within the hospital, with no neurological symptoms and MMSE ≥ 29. These were individually matched for sex and age at scanning to the CJD group.

MR imaging and analysis

Scans were performed at St. Mary's Hospital or the National Hospital for Neurology and Neurosurgery, London on 1.5 T Signa systems (GE Medical Systems, Milwaukee, USA). T1-weighted volumetric imaging was performed in the coronal plane, using a spoiled gradient echo technique (field of view, 24cm; 256 x 124 image matrix, acquisition parameters TR/TE: 51/4, 35/6, 35000/ 5000 or 1430/5400 depending on scanner location) providing 124 contiguous, 1.5 mm slices through the brain. Images were transferred to a Sun workstation (Sun Microsystems Inc., Mountain View, California, USA) for processing using the MIDAS image analysis program. Measurements on controls and patients were performed in a randomised

order by operators blinded to subject details. Initially, the whole brain was segmented from the rest of the MR image using a semi-automated technique[136]. Brain segmentations, were manually edited, to ensure accuracy, as illustrated in Figure 1.

Figure 1: Brain segmentation, illustration of one coronal slice



All measurements of cerebellar volume were performed on the coronal T1 volumetric images. The semi-automated segmentation programme allowed the viewing of the region, simultaneously in the coronal, sagittal and axial planes. A standard neuroanatomical atlas was used to define the borders of the cerebellum[137]. The first rostral slice was chosen as that in which cerebellar tissue was first visualised. An arbitrary point was used to determine when to start including the white matter of the cerebellar peduncles. This was taken as the most rostral section, which transected the superior vermis. Subsequent, alternate posterior slices were measured until the

cerebellar hemispheres were no longer seen. Thus the cerebellar vermis and tonsils were included. A signal intensity threshold for the cerebrospinal fluid (CSF)/cerebellar boundary was set at 60% of mean brain intensity which allowed reproducible automated separation of the cerebellum where it was bordered by CSF. The cerebro-cerebellar boundary was traced manually. Once completed, linear interpolation was used to fill the slices not directly segmented to give a final cerebellar volume.

Figure 2: Cerebellar segmentation, illustrated by one coronal slice

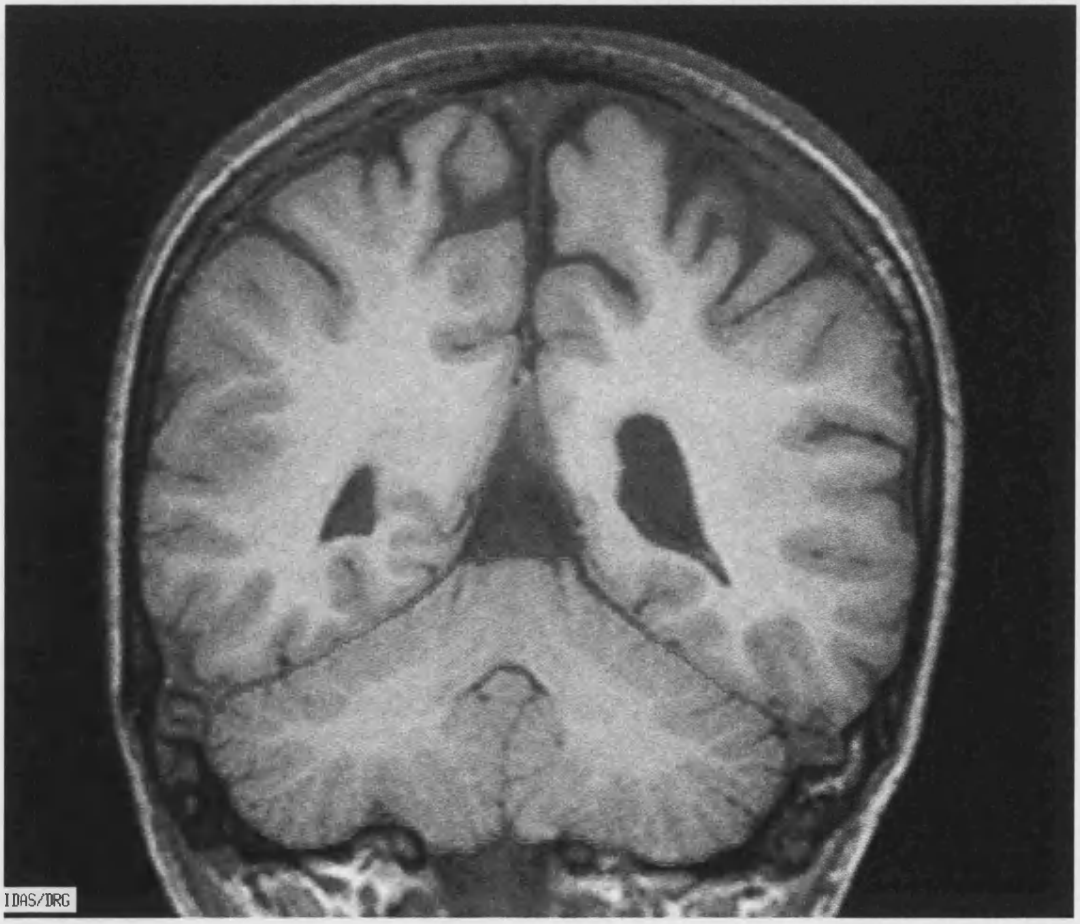


Figure 3: Cerebellar segmentation illustrated by one sagittal slice

The whole brain and cerebellar volumes were expressed as a proportion of the total intracranial volume (TIV), to correct for differences in the TIV. This allows cross-sectional normalisation to reduce inter-individual variation and is also used longitudinally to normalise for drifts in voxel dimensions. The technique used to measure the TIV has been described previously in detail and was performed by JW[138]. In summary, a semi- automated grey thresholding technique was used to outline the outer border of the dura on axial T1 images (using a standard threshold set at 33% of the mean intracranial signal intensity). Every 10^{th} slice was segmented with subsequent linear interpolation to give the TIV.

Two, serial volumetric images, acquired using the same scanner and identical imaging protocols were available for a subgroup of 5 familial cases. This allowed comparison of whole brain and cerebellar volume change over time in the patient and control groups. A fully automated registration algorithm was used to position the follow-up scan accurately onto the baseline image[139]. Registration of the images allowed the volume change between scans to be computed directly using a validated technique, the brain boundary shift integral (BBSI)[140]. Volume change was expressed as a percentage of baseline whole brain volume and annualised to give a rate of global atrophy.

Reproducibility Study

The reproducibility of the cerebellar volume measurements was assessed by the observer performing 2 separate volume measurements on scans from 10 subjects. These measurements were performed in a randomised, blinded manner over a period of several weeks.

Statistical Methods

Reproducibility was assessed by calculating means, within observer standard deviations and hence within observer coefficients of variation for each of the ten subjects. In addition, the overall mean and standard deviation of differences was calculated and used to construct 95% limits of agreement for the differences[141]. After expression as a proportion of TIV, whole brain and cerebellar volumes were compared between patients and controls using a paired Student's t test. The Student's t test was the appropriate test for two groups with matched pairs and continuous data.

The TIV corrected cerebellar volumes were regressed on age and sex in the control group allowing predicted values and the residual standard deviation to be calculated for the patient group. A *z* score ((actual patient value – predicted value)/ residual standard deviation) was calculated for each patient as a measure of the standardised difference between the actual TIV corrected volume and the predicted value in the patient group (Simple subtraction of control and patient volumes would not allow for the wide interindividual variation that exists in cerebellar volume). *Z* scores were compared between familial, sporadic and iatrogenic cases using unmatched t-tests. An unmatched t test was the appropriate significance test as the different subject groups were unmatched and the data was continuous. Analogously, *z* scores were derived from (brain – cerebellum) measurements.

Where longitudinal data were available, a brain boundary shift integral (BBSI) derived percentage change in volume over one year was compared for each patient and matched control[136]. The mean atrophy rate was calculated for the patient and control groups and atrophy rates were compared between patient and control matched pairs using the Wilcoxon rank sum test. The Wilcoxon rank sum significance test was appropriate for the two groups with matched pairs and ordinal data. Data were analyzed using Stata, release 6.0 (Stata Corporation, College Station, Texas). No attempt was made to calculate the annual rate of cerebellar atrophy in these familial cases. This would have been possible using this technique, if the cerebellum itself had been registered, but it was felt that the result would have limited use in clinical practice.

Results

The clinical features of this group of patients are summarised in table 34.

TIV and whole brain measurements were found to be highly reproducible (within measurer coefficient of variance expressed as a percentage, 0.16 (range 0.04-0.44) and 0.25 (range 0.04-0.49) respectively) as previously described[138]. The within measurer, coefficient of variance for cerebellar volume was 0.65%, confirming high reproducibility. The mean and standard deviation of differences in cerebellar volume were 899.81 mm^3 and 855.41 mm^3 giving 95% limits of agreement of -811.01 to 2610.63mm^3 (mean difference +/- 2sd of the differences) [141].

The mean volumes of the whole brain, cerebellum, and the rest of brain (whole brain - cerebellum), corrected for TIV, were statistically significantly smaller in the patient group compared with the controls (table 35).

Table 34: MR study: Clinical symptoms and signs

	Illness duration (months)	Clinical symptoms and signs							
		Premorbid personality disorder	Personality change/ depression	Cognitive decline	Myoclonus	Ataxia	Pyramidal signs	Extrapyramidal signs	Seizures
F20	24	+	+	+	-	+	-	-	-
F18	132	+	-	+	-	-	-	-	-
F10	84	-	+	+	+	+	-	-	-
F17	48	-	+	+	-	+	-	-	-
F15	18	-	-	+	-	+	-	-	-
F19	AS	-	-	-	-	+	-	-	-
F3	60	-	+	+	-	+	+	-	-
F9	24	-	+	+	-	-	-	-	-
S19	4	-	+	+	+	-	+	+	-
S5	5	-	+	+	+	+	-	-	-
S11	12	-	+	+	+	-	-	-	-
S12	2	-	-	+	+	-	-	-	+
S4	15	-	-	+	-	-	-	-	-
I1	3	-	-	+	+	+	-	-	-
I2	6	-	-	+	-	+	-	-	-

Table 35: Mean volumes corrected for Total Intracranial Volume (TIV)

Subject	CJD (n=15) 7 female	CONTROLS (n=15) 7 female	P value (paired t test)
mean brain volume (ml)	1115 +/- 279	1271 +/- 270	
mean brain/TIV	0.758 +/- 0.12	0.845 +/- 0.08	0.0002
mean cerebellar volume (ml)	117 +/- 35	135 +/- 34	
mean cerebellum/TIV	0.0798 +/- 0.018	0.0895 +/- 0.014	0.0024
mean volume (brain - cerebellum) (ml)	998 +/- 264	1137 +/- 242	
mean (brain-cerebellum)/TIV	0.678 +/- 0.12	0.755 +/- 0.08	0.0006

Figure 4 shows the *z* scores representing the standardised difference between the actual cerebellar volume and its predicted value by disease group. *Z* scores were significantly lower in the 2 iatrogenic patients than in either of the familial or sporadic groups (p=0.014, p=0.024). In these two cases, the disease had a characteristic cerebellar onset and rapid progression (case I1, illness duration = 7 months; case I2, illness duration = 11 months). Interestingly, both of these cases showed little or no cerebral cortical atrophy on macroscopic examination of the brain. Case I1 had marked atrophy of the vermis and superior cerebellar cortex. Case I2 had a moderate degree of folia atrophy over the whole cerebellum. Both cases showed marked loss of granular neurones, gliosis and spongiform change. Extensive spongiform change was noted in the molecular layer of the cerebellum in case I2 with the vermis and

flocculonodular lobes most affected. In both cases there was very strong PrP immunostaining in both the granular and molecular layers of the cerebellar cortex.

Figure 4: Corrected cerebellar volumes adjusted for age and sex

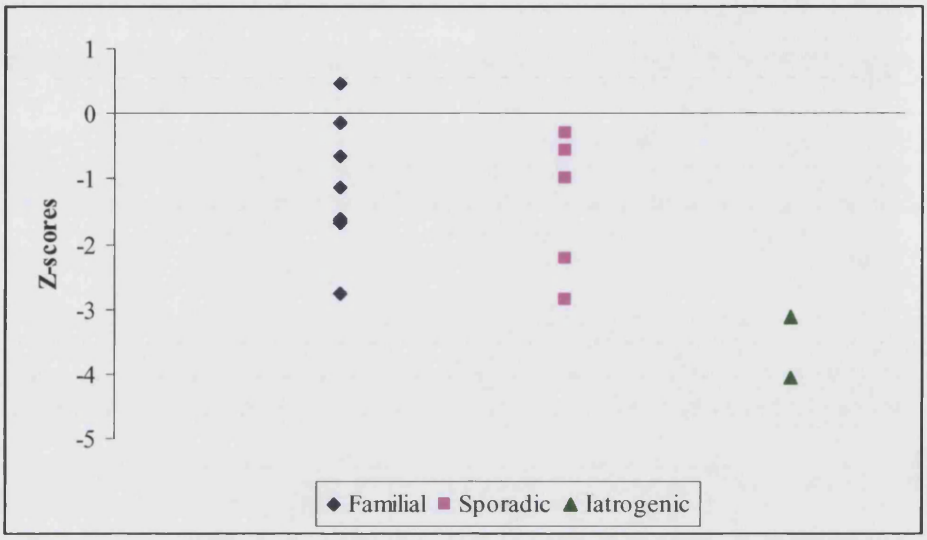
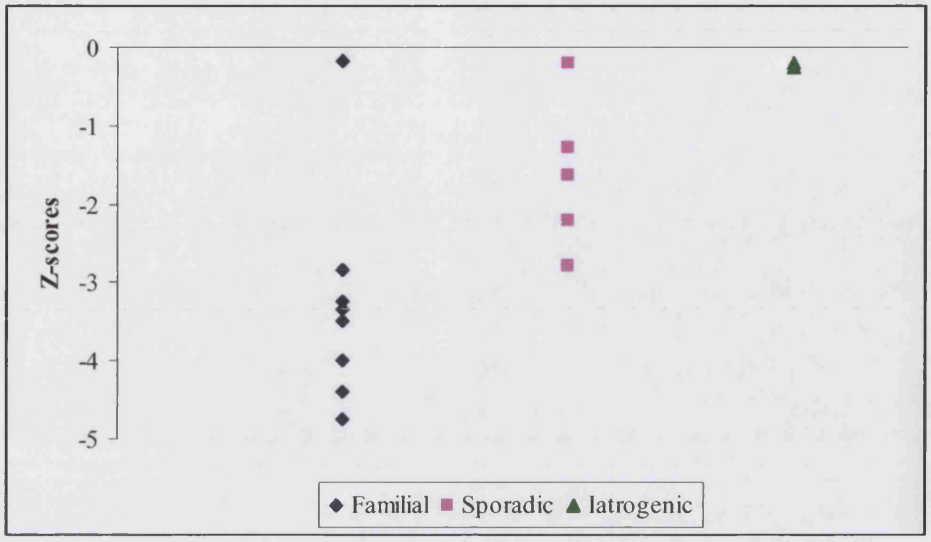


Figure 5 shows the z scores representing the standardised difference between the actual "rest of brain" volume (brain – cerebellum) and its predicted value by disease group. Z scores from the two iatrogenic patients were no different from those in the sporadic and familial groups (z scores –0.197 and –0.243 respectively), correlating with the absence of cortical atrophy seen at post-mortem.

Figure 5: Corrected (brain - cerebellum) adjusted for age and sex



Notably, in one sporadic case (case S9), where cerebellar signs were not a prominent feature, the measured corrected cerebellar volume was smaller than expected from the control data (z score –2.76). At post mortem, there was widening of the sulci within the posterior and middle part of the vermis and the posterior aspects of the cerebellar hemispheres. Microscopically, there was severe depletion of Purkinje and internal granule cells and sparse focal spongiosis of the molecular layer. PrP immunostaining was positive in the granular and molecular layers.

In other cases (F15, F19, O4, S11 and S12), where little or no difference was seen in measured cerebellar volumes from that expected from the control values, 3 out of 5 of the patients did not show prominent cerebellar features. Post mortem details are available for the two sporadic cases, S11 and S12. In case S11 (valine homozygous at codon 129, PrP type 1) there was marked cerebral atrophy with neuronal loss and gliosis. There was patchy spongiform change but no plaques seen in the cerebellum and although PrP immunostaining showed widespread positivity throughout the

cerebral cortex, cerebellar positivity was patchy but with reticular focal positivity in the molecular layer. Macroscopically, case S12 showed no obvious atrophy of the cerebrum or cerebellum. There was widespread neuronal loss, gliosis and spongiform change in the frontal, parietal, temporal and occipital lobes with fine vacuolation in the basal ganglia and thalami, but only mild spongiform degeneration in the molecular layer of the cerebellum, focal loss of Purkinje cells and gliosis. Immunostaining for PrP showed extensive positivity throughout the brain.

Although measures of both cerebellar and rest of brain volumes were significantly smaller for the group of eight patients with known prion mutations, the z scores calculated for the cerebellar volumes did not distinguish them from sporadic cases. Post-mortem details are available for cases one and three. Both cases had mild cerebral and cerebellar atrophy (of the vermis in case F10) visible macroscopically. Case F20 had abundant large eosinophilic plaques in the molecular layer of the cerebellum, and also more widespread plaques in the neocortex and subcortical white matter. In case F10 there was moderate spongiosis within the cerebral cortex and extensive deposition of PrP in the molecular layer of the cerebellum.

The cerebellar and whole brain volumes of three asymptomatic cases (one had mild truncal ataxia) with known mutations in the prion gene were not significantly differently from their matched control (using matched t test $p = 0.097$ and 0.19 respectively).

Further analysis of the standardised differences between the actual volumes of the rest of the brain (brain – cerebellum) and the predicted values by disease group showed

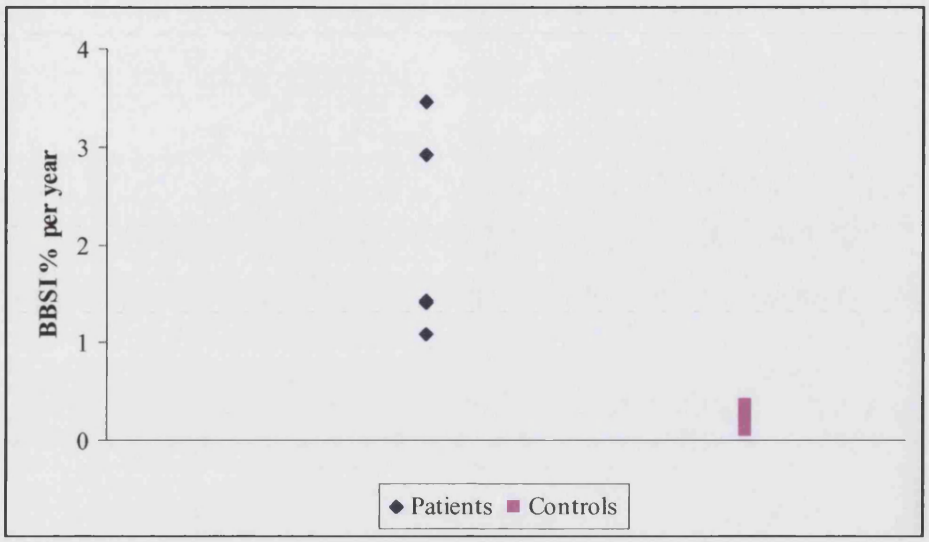
significantly lower z scores in familial forms of CJD, compared to sporadic and iatrogenic groups (p= 0.034, p= 0.008) (figure 5). This may suggest that the disease processes are as prominent in other brain areas, outside the cerebellum as within, in these cases.

Considering the subgroup of 5 familial cases with 2 scans several months apart, the mean rate of cerebral atrophy was 2.05% (+/- 2.12% 2sd) of brain volume per year for the CJD group and 0.246% (+/- 0.19%) per year for the control group (p = 0.043). The values for the percentage rate of change in BBSI per year in patient and control pairs are given in Table 36 and illustrated in Figure 6.

Table 36: Percentage rate of change of BBSI per year

Subject mutation	Illness duration at time of scan 1 (months)	Scan Interval		Difference BBSI %/year	
		Patient (months)	Control (months)	Patient	Control
102(F20)	0	24	14	1.4	0.22
144(F18)	120	9	12	1.08	0.28
144(F10)	60	13	32	2.92	0.11
144(F17)	36	9	13	3.45	0.37
144(F15)	12	6	11	1.42	0.24

Figure 6: Percentage rate of change of BBSI per year



Discussion

Rates of atrophy and patterns of tissue loss within cerebral substructures can be delineated from serially acquired, registered volumetric MR images. This technique has been applied in the study of AD to quantify tissue loss and therefore show disease progression[132] and also to demonstrate progressive cerebral and cerebellar atrophy in one case of familial CJD[133]. Quantification of whole brain and medial temporal lobe atrophy in AD allows the distinction between those with the disease and those with atrophy associated with normal aging, and also allows a correlation between the rate of volume loss and cognitive decline[140, 142&143]. These techniques may be of similar value in the diagnosis and monitoring of disease progression in CJD.

The first hypothesis was proven. Across the groups of sporadic, familial and iatrogenic prion diseases, it is possible to demonstrate significant cerebral and cerebellar atrophy with volumetric MR imaging, with scan interval ranging from 6 to 24 months. Further work is underway to assess the volume change in the cerebellum

of patients with Alzheimer's disease (AD). This will allow the evaluation of the usefulness of this tool in the differential diagnosis of CJD and AD especially in the elderly.

Volumetric MR image analysis, used cross-sectionally has limitations as a diagnostic tool as there is overlap in the range of whole brain and cerebellar volumes in CJD and control groups. Applying the technique longitudinally to registered, serial images allows calculation of the BBSI, which is a highly reproducible measure of atrophy. Volumes were corrected for the total intracranial volume which is essential not only to reduce individual variation when using the data cross-sectionally, but more importantly to allow for changes in scanner gradient calibration over time in the longitudinal study. Good quality, serial imaging is difficult to obtain in this patient group. The patients often tolerate MR scans poorly, they have movement disorders, for example, myoclonus and chorea, which introduce movement artefact and their clinical condition may deteriorate over a matter of weeks making repeat scanning inappropriate. Where serial imaging is possible, in those with familial disease, atrophy may be quantified only at the time of repeat imaging, six to twelve months from baseline, thus reducing the feasibility of the technique as an immediate diagnostic test. However the second hypothesis was proven. It was possible to quantify annual whole brain atrophy in a subgroup of patients with familial CJD.

In this subgroup of familial cases, there was one case with a P102L mutation (F20) in the Prion gene and four with 144 base pair insertions. The illness duration at the time of the first scan ranged from 0-120 months and the scan interval ranged drom 6-24 months. Case F20 was asymptommatic at presentation and over the two-year period

between scans; there was no measurable decline in general intellect. However, verbal and visual memory and frontal executive function became impaired over this time.

Cases F10 and F17, with the greatest measured annual rates of cerebral atrophy, both had severe decline in intellect with global deficits (very impaired memory, naming, visual perception and frontal executive function). Cases F15 and F18 had severe decline in intellect and frontal executive dysfunction but with some preservation in verbal memory and naming (and visuoperception, F15 only) until later in the illness course. Although there are similar rates of whole brain atrophy compared to those seen in patients with AD, this suggests that the pattern of cognitive decline in the familial CJD cases and therefore the distribution of atrophy in the brain may be distinct in these different diseases.

With the recognition of new prion diseases, such as vCJD, the search for disease modifying agents has a new impetus. Carefully conducted clinical trials in confirmed cases of CJD are necessary to test the effectiveness of these therapeutic agents. This requires well-validated, reproducible markers of clinical outcome, which can detect changes in disease progression in treated and placebo groups. Although cross sectional volumetric MR imaging may not be feasible as a diagnostic marker, quantification of rates of atrophy in the whole brain and cerebellum in CJD over time using MR may be suitable to monitor disease progression in therapeutic clinical trials.

MR spectroscopy in CJD

Introduction

Proton magnetic resonance spectroscopy (1H-MRS) is a non-invasive tool used in the quantification of neurometabolites in defined regions of the brain. It may be performed as part of a clinical MRI brain examination, in the same scanner if this is equipped with appropriate software. Use of this technique in the investigation of the prion diseases has been limited to date.

The earliest report of H1-MRS in human prion disease, to our knowledge, describes a 53-year-old female with biopsy proven sporadic CJD[144]. Seven months from illness onset, MR imaging showed mild cortical atrophy and hyperintense signal in the lentiform nuclei. Short TE 1H-MRS of the left parietal white matter showed a reduction in the N-acetylaspartate (NAA) peak by 40% and an increase in myoinositol (MI) of 30% compared to a normal age and sex matched control. The results were similar in the right parietal and frontal white matter regions. In the paramedian frontal and parietal grey matter, NAA alone was reduced by 30%. The authors correlate the reduction in NAA with the severe neuronal loss found in CJD and note that the metabolic alterations occurred in regions of the brain which appeared normal on structural MR imaging.

Subsequent published studies have used long echo time techniques. There is one report of 1H-MRS performed at an earlier stage in the illness course[145]. Imaging from two cases of sporadic CJD performed at three months and less than one month from symptom onset failed to show any significant change in metabolite concentrations when compared to results from two non-demented control subjects, using a region of

interest (ROI) incorporating the left and right parietal cortex and bilateral subcortical white matter. In one case, imaging was repeated at ten months revealing a drop in the NAA concentration in this region by 46%.

There are two further reports of the use of 1H-MRS in familial prion disease. Shyu et al describe a case with a point mutation at codon 210 (GTT to ATT), presenting with an unusual panencephalitic form of CJD with an early onset and long illness duration[124]. MR imaging at three months from symptom onset demonstrated increased T2-dependent signal intensity in the basal ganglia and thalami. Imaging twelve months later showed evidence of cortical thinning, diffuse signal change in the white matter and hypointense signal in the basal ganglia and thalami. 1H-MRS of the frontal region showed an absence of NAA, creatine (Cr) and choline. Konaka et al, 2000, report a 22 year old female with Gerstmann-Straussler-Scheinker (GSS) disease (P102L mutation) [146]. One year from symptom onset, MR imaging revealed mild atrophy of the cerebellar hemispheres, vermis and the cerebral cortex. Spectra from voxels placed in the frontal cortex, putamen, cerebellar vermis and hemispheres showed reduction in the NAA/Cr ratio in each region, including the frontal lobe, putamen and cerebellum; correlating with the neuropsychiatric features, and extrapyramidal and cerebellar signs. SPECT perfusion patterns were normal in the cerebrum and cerebellum in this case. The authors suggest that subtle changes in GSS may be discernible with 1H-MRS even in the early stages of the illness.

Pandya et al report short echo time 1H-MRS in one case of probable vCJD, twenty months from illness onset (after 93% of the total illness duration). The patient had bilateral increased signal in the pulvinar on T2 dependent images and a markedly

reduced NAA/Cr ratio ratio in the right pulvinar[147]. There was no quantification of MI ratios. Imaging data from two cases with biopsy proven sporadic CJD were also discussed. In both cases there was increased signal in the putamen and caudate nucleus on T2 weighted imaging and a reduction in the NAA/Cr ratio in the putamen using long echo time 1H-MRS. There was variable thalamic signal change reported on T2 dependent imaging not further investigated with 1H-MRS.

To further increase our knowledge of the diagnostic potential of short TE *in vivo* spectroscopy and any insight it may give into pathological changes in prion disease, we studied the spectroscopic features of three cases with probable vCJD, with comparative data for two cases with familial CJD, one with sporadic disease and eight normal control subjects.

Methods

A subgroup of five patients enrolled in the project, were recruited for further MR imaging (V2, V7, V14, O1 and O4; 2 male, 3 female mean age 30.6 years). Three cases were given a diagnosis of probable variant CJD with positive tonsillar biopsy. In the other two cases, a mutation was detected in the prion protein gene and the clinical symptoms and signs were thought to be compatible with the onset of familial disease. Data from these subjects were compared to those from a further case with biopsy proven sporadic CJD (age > 60 years) and one young, asymptomatic subject with a family history of prion disease and a mutation in the prion gene detected at presymptomatic testing. A further group of 8 age matched normal controls were recruited (3 male, 5 female; mean age 26.8 years).

Short echo time, single voxel 1H-MRS was performed using an automated point resolved spin echo localisation (PRESS) technique on a commercial clinical 1.5 T MR scanner (PROBE-Q, Signa Horizon EchoSpeed scanner, v 5.7 software, TR 2000ms, TE 30ms, 192 averages, General Electric Medical Systems, Milwaukee). All of the cases also had dual echo axial localisation images (axial inversion-recovery fast spin echo, 3mm thick slices, T1 = 300ms, TR = 3000ms, TE = 15ms). Spectra were acquired from voxels of interest (1-3 ml volume) selected in the left pulvinar region (postero-medial thalamus), the left caudate nucleus and the right frontal white matter. In these areas and with these voxel sizes, infringement on cerebrospinal fluid was not a problem. There was therefore no need to make corrections for atrophy. Metabolite ratios were determined using on-line software (PROBE-Q) and concentrations calculated off-line using validated frequency domain fitting technique, LC Model [Provencher] [148]. The T2 and PD-weighted localiser images were reviewed by a neuroradiologist, together with any existing structural MR imaging, i.e. axial T2 and proton density and volumetric images, to determine the presence of cerebral atrophy and pathological signal change in the patient and control groups.

Spectra were obtained using the same protocol in eight normal control subjects. Localiser images in this group were also reviewed for unsuspected structural abnormalities. All spectra were inspected visually. Metabolite ratios for the assigned resonances for N-acetylaspartate (2.01 ppm), Choline (3.2ppm), and myo-inositol (3.56ppm) were calculated relative to Creatine/phosphocreatine (3ppm) using PROBE Q. Concentrations of the metabolites, myoinositol [MI] and N-acetylaspartate-glutamate [NAA (G)] were calculated using LC Model. The repetition times were shorter than those normally used for quantitative measures in order to minimise

acquisition time. T1 effects may potentially lead to an underestimation of the concentrations calculated and so these were expressed using institutional units (IU). Metabolite concentrations and ratios were compared between the variant CJD and normal control groups using the Mann-Whitney U test. The Mann Whitney U test was the appropriate significance test, for non-parametric data, for two groups with different (unpaired) subjects.

Results

The clinical characteristics of the cases are given in Table 37. The H1-MRspectroscopy data for the variant cases and the normal controls are given in tables 38 to 40.

Table 37: MR spectroscopy: Clinical characteristics of the cases

Case	Illness duration (at time of assessment in months)	Clinical symptoms and signs							MRI	
		personality change/ depression	cognitive decline	myoclonus	ataxia	pyramidal signs	extra-pyramidal signs	sensory disturbance	atrophy	signal change
V2	14	1	1	0	1	1	0	1	0	thalamus and midbrain
V7	11	1	1	0	1	0	0	1	0	thalamus
V14	16	1	1	1	1	1	0	0	0	posterior &medial thalamus
O1	84	1	1	1	1	1	1	0	1	0
O4	23	1	1	0	1	1	0	1	0	mesial frontal
S9	4	1	1	1	0	1	1	0	0	0

There was a significant and dramatic, 2.5 fold (150%) increase in the concentration of MI, and a significant, 50% reduction in NAA in the left posterior thalamus of the three cases of probable variant CJD compared to the normal controls. This was consistent with a rise in the MI/Cr ratio and a fall in the NAA (G)/Cr ratio in this region. All three cases were reported to have the pulvinar sign on T2 MR structural imaging, confirmed on review of the localisation images. The calculated mean MI/NAA ratio for the vCJD cases was 5.6 times greater than that for the normal controls (mean MI/NAA vCJD = 2.06, standard deviation (sd) = 0.501; normal controls = 0.37, sd =0.092).

There was a significant increase in [MI] and the MI/Cr ratio in the right caudate in the two cases where this region was examined although only one case showed a significant reduction in NAA (G). No signal change was reported in this region on T2 MR imaging. Data from the frontal white matter were only available for one of the three variant cases. These showed a significant decrease in the NAA (G)/Cr level from the PROBE measurements only. No corresponding white matter signal abnormality was detectable on T2 weighted images.

The two young familial cases showed different patterns of abnormality with H1-MRS. Case O1 showed a significant increase in MI and the MI/Cr ratio in the left thalamus. O4 did not show any abnormality in this area. In neither case was any thalamic signal abnormality apparent on T2 weighted images. Only O4 tolerated further imaging in the caudate and frontal regions. There was a significant reduction in NAA (G) in the caudate. The value for the concentration of creatine in this region was below the normal range and so meaningful interpretation of metabolite ratios was not possible.

In this case there was also a significant reduction in NAA (G) (LCModel) and NAA/Cr (probe) in the right frontal white matter, in an area where increased signal had been reported on T2 axial MR images.

The young, asymptomatic subject, with a known mutation in the PRNP gene, had normal T2 axial and volumetric MR imaging. There was however, a significant increase in MI and the MI/Cr ratio in the right frontal white matter. There was no history of onset of behavioural features or other clinical symptoms or signs. H1-MRS in the thalamus and caudate was normal.

H1-MRS was performed in one case with classical, sporadic CJD, confirmed histologically at post mortem examination. MR imaging performed 4 months from the onset of symptoms showed high signal in the right caudate nucleus and less prominently in the right putamen. Minor high signal lesions were seen in the white matter, felt to be of no clinical significance and unremarkable for the patient's age. H1-MRS showed a significant increase in MI and a significant reduction in NAA(G) in the left thalamus (there was a significant reduction in the NAA/Cr ratio taken from the probe measurements only). There was also a significant reduction in NAA(G) in the frontal white matter. Interpretation of ratios to creatine was difficult as the creatine value was outside the normal range in this region. In this case PM examination revealed widespread, moderate cortical atrophy, greatest in the frontal cortex (the cingulate gyrus was most affected and the occipital cortex the least). In the thalamus, there were several foci of spongiosis with granular PrP staining. The caudate nuclei showed severe reactive astrocytosis, but minimal vacuolation or PrP deposition. Reactive astrocytosis was seen throughout all layers of the neocortex, with spongiosis

at the junction of layers I and II. No PrP plaques were identified. The main PrP immunoreactivity load occurred in the temporal lobe, thalamus and cerebellum.

Table 38: Metabolite concentrations in the left thalamus (institutional units (iu) given)

	Variant mean (2sd) **n=3**	normal control mean (2sd) **n=8**	P value
MI (iu)	7.53	2.93	0.014
	(1.36)	(0.85)	
MI/Cr	1.38	0.62	0.014
	(0.30)	(0.22)	
MI/Cr (probe)	1.05	0.56	0.014
	(0.26)	(0.13)	
NAA(G) (iu)	3.78	8.05	0.014
	(1.44)	(1.91)	
NAA(G)/Cr	0.69	1.70	0.014
	(0.22)	(0.48)	
NAA/Cr(probe)	0.59	1.60	0.014
	(0.36)	(0.35)	

Table 39: Metabolite concentrations in the right frontal white matter

(institutional units (iu) given)

	Variant mean (2sd) **n=1**	Normal control mean (2sd) **n=8**
MI (iu)		2.27
		(1.68)
MI/Cr		0.68
		(0.41)
MI/Cr (probe)	0.69	0.69
		(0.22)
NAA(G) (iu)	6.98	6.58
		(0.96)
NAA(G)/Cr	1.73	2.13
		(0.71)
NAA/Cr(probe)	1.34	2.01
		(0.40)

Table 40: Metabolite concentrations in the right caudate nucleus (institutional units (iu) given)

	Variant mean (2sd) **n=3**	Normal control mean (2sd) **n=8**	P value
MI (iu)	7.04	3.09	0.040
	(2.44)	(2.17)	
MI/Cr	1.22	0.54	0.040
	(0.24)	(0.42)	
MI/Cr (probe)	0.99	0.56	0.044
	(0.50)	(0.22)	
NAA(G) (iu)	5.77	6.77	1.000
	(4.14)	(1.60)	
NAA(G)/Cr	1.00	1.19	0.143
	(0.56)	(0.33)	
NAA/Cr(probe)	1.11	1.31	0.242
	(0.34)	(0.44)	

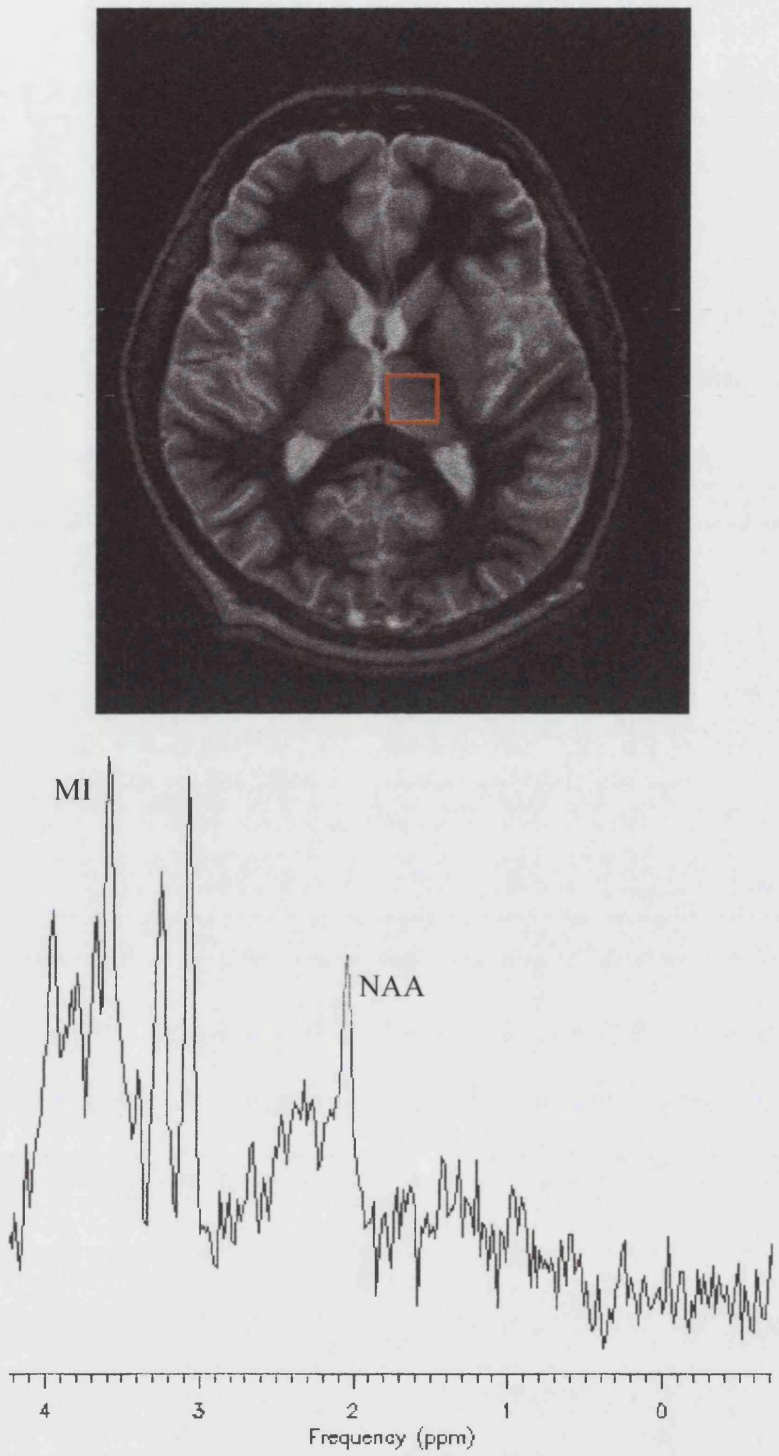


Figure 7: Case V2 (vCJD) left thalamus

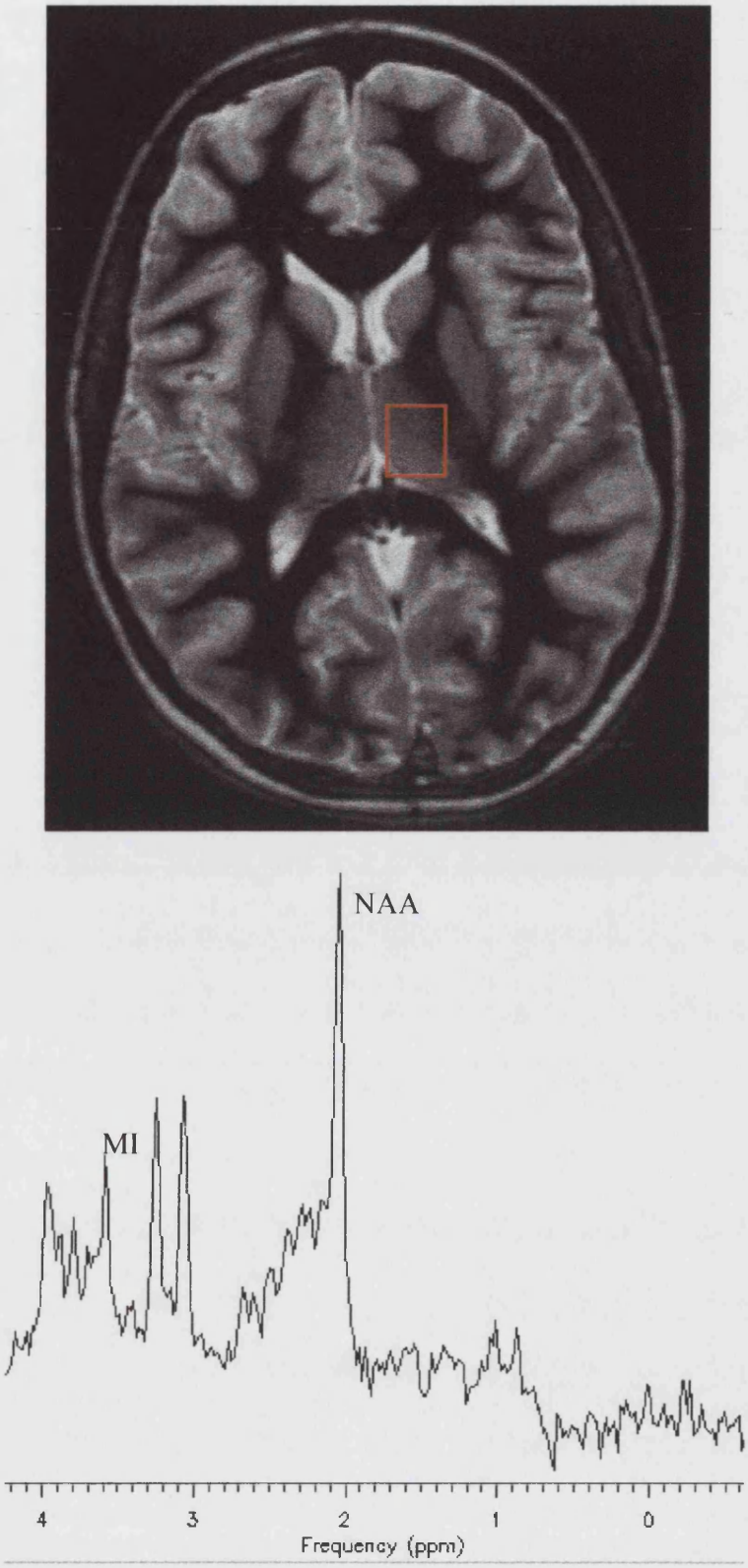


Figure 8: Normal control left thalamus

Discussion

The pathological significance of the marked increase in myo-inositol and very low levels of NAA in the thalamus of these cases with vCJD is uncertain but may reflect the severe astrogliosis and neuronal loss which are seen at post mortem in the pulvinar nuclei in this condition. These changes are thought to produce the characteristic bilateral pulvinar hyperintensity that has been described on T2 dependent sequences in a large number of cases with variant CJD[109]. The grey matter changes seen with 1H-MRS are similar to but far more marked than those widely reported in other degenerative dementias. An increase in MI of 15-20% and a decrease of NAA of 10-15% has been reported in grey matter in AD[149]. By comparison, in all three cases of vCJD in this study, there was an approximate 150% increase in the mean MI concentration and approximate 50% reduction in NAA concentration detected in the thalamus. The combined effect gives over a 5-fold increase in the mean MI/NAA ratio for vCJD compared to normal subjects. There was a significant increase in MI in the right caudate of the two cases with vCJD in whom this region was tested. 1H-MRS revealed more extensive abnormalities than those seen on structural sequences and also demonstrated different patterns of metabolic change in the subtypes of prion disease, possibly reflecting differential involvement of structures within the brain. The two cases of familial CJD were originally referred with symptoms and signs suggestive of variant CJD. Both cases were young (ages 28 - 30 years) and fulfilled the diagnostic criteria for possible vCJD prior to genetic testing. Interestingly, neither of these cases had the same profile with H1-MRSpectroscopy. One case did show a significant increase in MI in the thalamus but with a normal NAA concentration in this area. The other case had normal spectra in the thalamus but a reduction in NAA in the frontal white matter and the right caudate nucleus. The study of larger groups

is needed to clarify the consistency of this difference in pattern of metabolite change between subtypes of prion disease.

Many functions have been attributed to MI to account for changes in concentration with disease[150]. Glial cells are thought to contain high levels of MI and so this may act as a marker of glial cell numbers. Other suggested roles include that of an osmoregulator, an intracellular messenger or as a detoxification agent via glucuronate, a breakdown product. NAA concentration is thought to act as a marker of neuronal viability. Mitochondrial phosphorylation and rates of NAA synthesis have been correlated. Reductions in NAA have been documented in AD in the absence of detectable cerebral atrophy leading to suggestions that a reduction in NAA may indicate an alteration in mitochondrial function or neuroinflammation in neurons that are still viable, rather than a loss of neurons. All three of the cases of vCJD in this study had the pulvinar sign on T2 weighted images suggesting profound reactive astrogliosis in this region. It could be postulated that the dramatic increase in MI in this region could simply be attributed to the high MI content of these glial cells.

One of the limitations of this part of the study was the small number of patients and their late presentation such that all of the cases had moderately advanced vCJD at the time of imaging. Single voxel MRS techniques require the patient to remain still for consecutive, approximate seven minute periods for the acquisition of data for each region. Patients presenting at an advanced stage of the illness were less able to tolerate this. However, the magnitude of the metabolic derangement in these cases suggests that it may be possible to detect abnormalities earlier in the disease course. Significant metabolic abnormalities were demonstrated in regions where signal was

normal on T2 weighted sequences. The presence of regions with an abnormality in myo-inositol concentration with normal NAA suggest that as with other conditions e.g. Down's syndrome, elevation in MI may precede NAA loss associated with neuronal loss or dysfunction[151]. Significant MI abnormality was also demonstrated in one currently asymptomatic gene carrier. All of these findings suggest that short echo time 1H-MRS may have a role in the early diagnosis of the prion diseases and that further studies to explore this potential are warranted.

STUDY II: THE MANAGEMENT OF YOUNG PEOPLE WITH DEMENTIA

Introduction

Many of the problems faced by young people diagnosed with variant CJD and their families are not unique. They are shared by others with Alzheimer's disease, frontotemporal degeneration and other causes of early onset dementia. All become unwell at a time that affects their young families, employment prospects, finances and generally their life at home. They can undergo difficult behavioural changes, accompanied by a loss of the cognitive and physical ability to cope with the activities of daily living and become increasingly reliant on spouses or parents for everyday care. Carers are unable to envisage or predict the potential difficulties in caring for someone with this relentlessly progressive disease and education and practical forward planning may alleviate many problems. Health care professionals have a duty, not simply to diagnose an illness and alleviate symptoms but also to provide ongoing advice and support in all aspects of management of the patient and their family. This is particularly important for the prion diseases where much time has to be invested in the explanation of this little understood and often misconceived illness. There needs to be careful explanation of issues surrounding infection control for example in dental and surgical practice; measures to prevent transmission via blood or organ donation and genetic screening to exclude a hereditary cause.

One of the major concerns of families is the likelihood of vCJD occurring in siblings or children of affected family members who may have shared meals in childhood or possibly been exposed in utero or via breast feeding. Although there is currently no evidence to date to support an increased risk to siblings or of vertical transmission, the

potential risks are not quantifiable and so much counselling time is often spent dealing with such issues.

Seeing at first hand the difficulties faced throughout the diagnostic and management phases of this illness by exhausted and distraught families prompted a closer look at how young people with dementia and their families are managed across the UK. There have been concerns that whilst young people would naturally be referred to general adult or paediatric psychiatrists with early onset dementia, it is old age psychiatrists who have particular experience in the management of patients with dementia with liaison with professionals in the community. There is a risk that patients may fall between these and neurology specialities resulting in incomplete care. As a result of these concerns the Royal College of Psychiatrists has made recommendations for service provision for young people with Alzheimer 's disease (AD) and other dementias[152]. They propose that each district should have one named consultant responsible for the service, suggesting old age psychiatrists are best placed to fulfil this role, whilst acknowledging the need for close collaboration with a range of specialists.

Although the proposals are welcomed, there were also concerns that patients may be inadequately investigated if referral to neurologists was incomplete[153-156]. The task force initiated by the European Federation of Neurological Societies (EFNS) recommends, that neurologists should have a clear role in the management of dementia[157].

We therefore conducted a survey to assess current stated UK practice in the diagnosis and management of younger people with dementia. Our main objective was to determine how patients are investigated and what support and follow up is offered.

Method

The questionnaire (see appendix II) was sent to all consultant neurologists and old age psychiatrists in the UK, identified from lists supplied by the Royal College of Psychiatrists and Association of British Neurologists. Reminders were sent after six weeks to non-responders. Questions required either yes/no or graded (i.e. always, often, sometimes or never) answers.

Statistical Analysis

Statistical analysis was performed using STATA6 (Stata Statistical Software: Release 6.0 for Windows, Stata Corporation). Where responses were compared between consultant neurologists and old age psychiatrists, P-values were calculated using the 2-sided Fisher's exact test. The Wilcoxon rank sum test was applied to compare the trends of responses given, where replies were graded.

Results

A summary of the main results is given in table 41. Overall, 64% of the population surveyed responded, comprising 67% (212/318) of consultant neurologists and 62% (215/346) of consultant old age psychiatrists. All subsequent figures are given as a percentage of those specialists who responded to each question.

The number of new referrals with young onset dementia to neurologists and old age psychiatrists was comparable. Where it was indicated that a specialist dementia service was available, 80% (95% confidence interval 71-87%) of neurologists refer to such a centre compared to 37% (22-53%) of old age psychiatrists ($P<0.0001$). Twenty-one percent of consultant neurologists (16-28%) refer to old age psychiatry services in comparison to 60% of old age psychiatrists (52-67%) who refer to a neurologist.

Of those neurologists who are not part of and do not refer to a specialist dementia service and who state they do not receive referrals from old age psychiatrists ($n = 75$), 23% (14-34%) refer to an old age psychiatrist. 77% therefore do not involve an old age psychiatrist in their patient management. Of the equivalent group of old age psychiatrists not working as part of or referring to a specialist team and who do not receive neurological referrals ($n = 71$), 51% (39-63%) do not refer to a neurologist. Where no regional centre was available for referral, 87% (77-93%) of neurologists and 84% (76-90%) of old age psychiatrists stated that they would refer to one if it became available ($P=0.68$).

A comprehensive history, including a family history, details of personality change and somatic symptoms was taken by the majority of neurologists and old age psychiatrists. In contrast, significantly more old age psychiatrists obtained an independent history from a carer and assessed symptoms of depression and changes in driving performance (see table 41).

Reported rates of performing physical examinations were statistically significantly higher amongst neurologists, with 70% (64-77%) and 98% (95-99%) *always* performing general physical and neurological examinations respectively, compared to 57% (50-64%) and 50% (43-57%) of old age psychiatrists (P=0.0011 and P< 0.0001). Comparing the subgroup of old age psychiatrists practicing without liaison with neurologists and specialist services (n=56), with neurologists, only 54% (40-67%) and 45% (32-59%) of these, *always* performed general and neurological examinations respectively (P=0.011 and P<0.0001).

Although the use of investigations such as, full blood count, vitamin B12, electrolytes, renal, liver and thyroid function was comprehensive between the groups, other important tests, for example, measures of plasma viscosity (for example, erythrocyte sedimentation rate, ESR) and syphilis serology were requested by statistically significantly more neurologists than old age psychiatrists (ESR: neurologists 92% (87-95%), old age psychiatrists 78% (72-84%), P = 0.0001). The use of structural imaging overall was comparable; although only 79% (72-84%) of neurologists and 76% (69-81%) of old age psychiatrists indicated that they *always* perform either a CT or MRI brain scan (P=0.37).

Only 37% (30-44%) of neurologists *always* and 32% (25-39%) *often* use EEG and 25% (19-31%) *always* and 34% (27-41%) *often* arrange cerebrospinal fluid (CSF) examination. Significantly fewer old age psychiatrists arrange these investigations (P<0.0001), and in particular, of the subgroup of old age psychiatrists who practice without liaison with neurologists, 77% (63-87%) *never* arrange CSF examination.

Participants were asked if carers were given an opportunity to see the doctor in the absence of the patient. Sixty-eight percent (61-74%) of old age psychiatrists *always* managed this compared to 50% (43-57%) of neurologists, (P=0.0001). Forty-four percent (37-51%) of old age psychiatrists, compared to only 18% (13-24%) of neurologists have a specialist nurse available in their unit to provide support and information to patients and carers (P<0.0001).

Significantly more old age psychiatrists, 64% (57-70%), compared to 37% (31-44%) of neurologists, always provide information about support groups such as the Alzheimer's Society (P<0.0001). Again significantly fewer of the subgroup of neurologists acting without liaison with old age psychiatry services, give such information and support, when compared to old age psychiatrists (P=0.0001). Advice given regarding informing the driving and vehicle licensing association (DVLA) was comparable. Significantly more old age psychiatrists involve Community Psychiatric Nurses (CPN), in managing their patients in the community, with 46% (39-53%) indicating that they *always* refer, compared to 6% (3-10%) of neurologists (P<0.0001). Those neurologists practicing without involving old age psychiatry services, in line with neurologists as a whole, were also statistically significantly less likely to involve CPN than old age psychiatrists (P<0.0001).

Finally, consultants were asked to grade how often they discussed drug treatments and trials with their patients. Significantly more old age psychiatrists *always* discuss drug treatments, 52% (45-59%) compared to 38% (32-45%) of neurologists (P<0.0001). Old age psychiatrists were also more likely to discuss therapeutic trials (P=0.0074). Fifty-two percent (45-59%) of old age psychiatrists compared to only 31% (25-38%)

of neurologists prescribe acetylcholinesterase inhibitors as per guidelines (P<0.0001). Of the prescribing specialists, only 58% (49-67%) of neurologists, compared to 98% (94-99%) of old age psychiatrists monitor patients after prescription (P<0.0001).

Table 41: Summary of the key responses from consultant neurologists and old age psychiatrists

		N	Always		Often		Sometimes		Never		P value
			n	(%)	n	(%)	n	(%)	n	(%)	
HISTORY											
driving ability	CN	210	125	(60)	59	(28)	26	(12)	0	(0)	0.0082
	COAP	211	151	(72)	44	(21)	16	(8)	0	(0)	
symptoms of depression	CN	211	188	(89)	20	(9)	3	(1)	0	(0)	0.011
	COAP	211	202	(96)	7	(3)	2	(1)	0	(0)	
independent history from carer	CN	211	177	(84)	32	(15)	2	(1)	0	(0)	0.0021
	COAP	211	197	(93)	14	(7)	0	(0)	0	(0)	
EXAMINATION											
general	CN	210	148	(70)	36	(17)	26	(12)	0	(0)	0.0011
	COAP	211	120	(57)	43	(20)	36	(17)	12	(6)	
neurological	CN	209	204	(98)	5	(2)	0	(0)	0	(0)	<0.0001
	COAP	208	103	(50)	55	(26)	36	(17)	14	(7)	
INVESTIGATION											
imaging	CN	196	154	(79)	41	(21)	1	(1)	0	(0)	0.37
	COAP	202	153	(76)	39	(19)	9	(4)	1	(0)	
FOLLOW UP											
community psychiatric nurse	CN	199	12	(6)	45	(23)	90	(45)	52	(26)	<0.0001
	COAP	209	96	(46)	102	(49)	10	(5)	1	(0)	
information on support groups	CN	210	78	(37)	82	(39)	39	(19)	11	(5)	<0.0001
	COAP	211	134	(64)	62	(29)	15	(7)	0	(0)	

CN – consultant neurologist; COAP – consultant old age psychiatrist

Discussion

I devised this survey to investigate my concerns that people with young onset dementia may experience delays in clinical investigation and diagnosis and inefficient management due to the lack of a defined age-appropriate specialist service to address their needs. I was expecting to show that original referral to a general adult (or paediatric) psychiatrist may mean a delay in referral to a neurologist and a delay or absence of a full neurological investigation. Simlarly, direct initial referral to a neurologist may mean a delay or absence of referral to old age psychiatry services and hence a lack of appropriate community followup. Whilst some areas of the country have multidisciplinary dementia services with input from neurologists, old age psychiatrists, CPNs and social workers, working from one centre, this is not the case everywhere.

There was a good response to the postal survey. Analysis of referral patterns confirmed that the ideal of full collaboration between consultant neurologists and old age psychiatrists is not achieved. There are young patients with dementia managed by consultant neurologists without liaison with old age psychiatry services and vice versa. This is important because the survey illustrates (as I expected) that consultant neurologists and old age psychiatrists investigate and manage these patients differently. More consultant old age psychiatrists take details of symptoms of depression and changes in driving ability but only half always perform a neurological examination. Fewer than half of the subgroup of consultant old age psychiatrists, who do not collaborate with neurologists, perform a neurological examination implying that this task falls to the general practitioner in many cases. The results also suggest that fewer consultant old age psychiatrists arrange key serological investigations.

EEG and CSF examinations are arranged more frequently by consultant neurologists but are not routinely used by either specialist. This is expected as the role of these investigations may be in cases where there is a certain clinical suspicion or unusual presentation (in accordance with the EFNS guidelines). In the American Academy of Neurology dementia guidelines, lumbar puncture is not suggested as a routine study, but is recommended in a person with dementia under 55 years of age[158].

The Royal College of Psychiatrists have published a consensus statement on the assessment and investigation of elderly people with cognitive impairment[159]. This has been updated and future work will look at broadening the result to treatment, management and working with voluntary agencies, primary care and other professions allied to medicine, including social workers and community psychiatric nurses[160]. In a retrospective case note study[161], all cases of potentially reversible intracranial pathology were detected if these guidelines for brain imaging were applied. In a postal survey aimed at comparing the practice styles of US and UK neurologists, 98% of US and 97.7% of UK neurologists indicated that they would order a neuroimaging study for an elderly patient presenting with dementia[162]. In our study, neither group of specialists indicated that they would always perform imaging in a case with young onset dementia. However this may be because a scan is performed prior to referral. The recommendation to neurologists of the European task force is that neuroimaging should be performed once in all cases of dementia referred to a neurologist[157].

The survey further reveals that more consultant old age psychiatrists give carers the opportunity to speak to them in the absence of the patient and a significantly greater percentage have a specialist nurse available. The former may be due to time

constraints in neurology clinics. A greater proportion of consultant old age psychiatrists give advice on support groups and information on matters such as power of attorney. Although the practice of informing patients about their responsibilities of instructing the DVLA was comparable between old age psychiatrists and neurologists, the number regularly doing so was lower than expected. Significantly more old age psychiatrists involve community psychiatric nurses in follow up, probably reflecting their expertise in the management of patients with behavioural problems in the community. The survey also importantly highlights that a larger proportion of old age psychiatrists when compared to neurologists, are involved in the prescription and monitoring of acetylcholinesterase inhibitor therapy.

Recommendations to neurologists from the European task force regarding the diagnosis and management of people with dementia should assist the development of local guidelines within neurology, psychiatry and specialist dementia services across the country. There are some specific areas where UK practice differs. It is recommended that all patients and carers should be asked about driving and that neuroimaging should be performed once in all young patients with dementia. More importantly though, the study shows that the assessment and management of patients with young onset dementia in the UK would be exemplary if the skills of both neurologists and old age psychiatrists were employed in the care of each patient. Clear standards are available for the diagnostic assessment and investigation of suspected dementia by Specialist Old Age psychiatry services[160], including guidelines from NICE regarding responsible prescribing. Consideration should be given to how the standards set in the National Service Framework for Older People[163], regarding

the person centred approach to care, could be extended to younger people with dementia.

The survey did not investigate the role of palliative care specialists in the care of patients with variant CJD. This crucial role did become apparent during the study period and with hindsight it would have been informative to investigate the current involvement of palliative care teams, by neurologists and old age psychiatrists. The CJD Surveillance Unit in Edinburgh, have reported the findings of a study of needs, from the perception of families caring for a relative with vCJD[164]. In depth interviews with families of 19 cases illustrated how difficult it was to find a suitable place to provide terminal care. Where available, specialist palliative care was of a very high quality and it was recommended that palliative care specialists be involved wherever possible.

In this project, most of the cases referred with possible vCJD were originally seen by their GP (mean six months from illness onset), with onward referral to a neurologist or psychiatrist on average 12 months from disease onset (mean ten and twelve months respectively). It would seem that to make an impact on early diagnosis, it is vital for general practitioners to have a high index of suspicion for vCJD to precipitate onward referral to specialist services with the minimum delay.

CONCLUSIONS

This project has involved the detailed study of 21 patients referred to two specialist centres with suspected vCJD. Fifteen cases were subsequently confirmed to have definite or probable disease as per diagnostic criteria. Key techniques of neuropsychology assessment, neuropsychiatric profiling, volumetric MR imaging and MR spectroscopy were employed to further characterise the illness and to assess their individual role as tools in the early distinction of vCJD from other diseases.

Detailed neuropsychiatric assessments confirmed the high level of symptoms of depression in the patient group, albeit at a moderately advanced stage of the illness. Importantly, whilst carers stated that these symptoms were present at an early stage, they felt these were uncharacteristic of the patient and often other symptoms were present to which insufficient importance was attached to prompt a diagnostic challenge e.g. mild gait disturbance, vague sensory abnormalities, mild cognitive impairment or even difficultly with micturition. One important lesson therefore, is to emphasise the need for a high index of suspicion for vCJD in young people with uncharacteristic symptoms of depression and other mild but unexplained cognitive, sensory or movement problems.

Other psychiatric features of vCJD were characterised. These included evidence of thought disorder, most commonly simple delusions of theft or suspicion, misidentifications, for example, misrepresentation of television images and behavioural features. The latter comprise uncharacteristic aggression, altered sleep pattern and emotional lability. However the ultimate distinction from other

diagnoses, as illustrated by all but one of the six cases that did not have vCJD, was the failure to develop characteristic neurological signs and the relentless progression to increasing disability and eventually akinetic mutism.

Detailed neuropsychology assessment has confirmed that moderate to severe intellectual decline is characteristic of vCJD and that this may occur as an early feature of the disease i.e. less than six months from illness onset. Although the decline generally affected all cognitive domains, with verbal and visual memory impairment, nominal and frontal executive impairment, only a minority of the vCJD patients, as a group, presented with perceptual impairment compared to half of those with sporadic or familial forms of prion disease. The proportion of patients presenting with nominal impairment was significantly lower in those with familial disease compared to variant and sporadic forms. These results emphasise again that evidence of progressive cognitive decline and the pattern of loss should be sought early, particularly in young people with depressive symptoms as this may prompt early investigation of an organic cause.

Proton MR Spectroscopy is a simple, non-invasive tool that may be a valuable adjuvant to MR volumetric imaging in the study of vCJD. In a limited group of patients with vCJD, a dramatic increase in MI and loss of NAA were detected in the posterior thalamus. This may reflect the severe astrogliosis and neuronal loss seen at post mortem in the pulvinar in this condition and the magnitude of the metabolic derangement suggests that abnormality may be detectable early in disease. The patterns of abnormality detected with MR spectroscopy differed amongst sporadic, familial and acquired forms of prion disease, which may reflect the differential

involvement of brain structures. There is some evidence that MI elevation may precede the loss of NAA, which is associated with neuronal dysfunction. MI abnormality was also detected in an asymptomatic gene carrier, which provides further hope that short echo time MRS may play a useful diagnostic role in the future.

Although insufficient, good quality, serial registered volumetric MR images were obtained from the patients with vCJD during the project, to allow the quantification of cerebral volume change over time, this technique was applied in a group of five patients with familial disease. The mean annual rate of cerebral atrophy calculated (2.05% of brain volume) is comparable to that seen in patients with AD. It would therefore seem appropriate to use this technique to monitor disease progression and to evaluate the effectiveness of future therapies once problems with patient tolerability are overcome. Once the effectiveness of a measure is established, the ethical considerations surrounding the use of sedation and general anaesthetics in people with cognitive impairment can be fully addressed.

The project was concluded with the analysis of a National survey to assess the broader picture of the investigation and ongoing management of young people with dementia across the UK. This highlighted the complexities of the diagnostic process and the many professional disciplines involved in the management of patients in the community. A multidisciplinary team approach involving both the expertise of neurologists and old age psychiatrists is necessary to ensure thorough investigation and follow up in all cases. Continued vigilance is necessary for unusual presentations of neurodegenerative diseases as the prion diseases may take different forms in older age groups and in those with other genetic profiles. Ultimately however, a swift

diagnosis lies with all medical practitioners having a high index of suspicion for vCJD and paying close attention to detail when history taking and during physical examination. Unexpected findings will then prompt the diagnostic possibility.

The project was limited mainly by the small numbers of cases referred with vCJD, over the study period. Referral was limited in part due to an understandable reluctance of patients' families to allow their spouse or child to travel, sometimes a fair distance from home for further investigation of the disease at a tertiary referral centre. This was increasingly the case as the pattern of the disease became more widely recognised, diagnostic criteria were established and neurologists and psychiatrists became more ready to make the diagnosis locally. Cases were referred at a moderately advanced stage of the illness and this limited all aspects of the project. It was not possible to directly establish the early neuropsychology profile of the subjects as most were too severely affected to complete complex neuropsychology tests. The study of psychiatric symptoms was limited by an inability of the patient to participate in most of the tests and so the information recorded is from in depth discussion with carers only. It was not possible to perform serial volumetric MR imaging to quantify cerebral and substructure atrophy in these cases, as all were unable to remain motionless within the scanner for the time required. The study has prompted much discussion around informed consent for research procedures from those with a neurodegenerative disorder. This is particularly important if the debate considers the use of sedation or anaesthesia to allow for detailed, time consuming research imaging protocols, which could encompass volumetric imaging, DWI and 1H-MRS. These issues will need to be given much thought to ensure the

effectiveness of future studies to look at early diagnostic tools whilst giving maximum consideration to the wellbeing of the patient and their family.

During the course of this project I have gained experience of, not only the characterisation of a novel illness, but also the immense political, economic and social impact of a rare but potentially devastating medical and social problem. The full impact on medical practice is only slowly being realised as concepts of potential transmission via medical procedures are considered. We are learning as clinicians to reconsider the safety of our practice, the true urgency of some operative procedures, and to rethink our use of many therapeutic products. One positive outcome is the move towards a more open and questioning society, which challenges practices within health care, the food and agricultural industries and local and National government.

REFERENCES

1. Britton TC, Al-Sarraj S, Shaw C, Campbell T, Collinge J. Sporadic Creutzfeldt-Jakob disease in a 16-year old in the UK. *Lancet* 1995; 346: 1155.

2. Bateman D, Hilton D, Love S, Zeidler M, Beck J, Collinge J. Sporadic Creutzfeldt-Jakob disease in an 18-year-old in the UK. *Lancet* 1995; 346: 1155-1156.

3. Tabrizi SJ, Scaravilli F, Howard RS, Collinge J, Rossor MN. Creutzfeldt-Jakob disease in a young woman. *Lancet* 1996; 347: 945-48.

4. Zeidler M, Johnstone EC, Bamber RWK et al. New variant Creutzfeldt-Jakob disease: psychiatric features. *Lancet* 1997; 350: 908-10.

5. Zeidler M, Stewart GE, Barraclough CR et al. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. *Lancet* 1997; 350: 903-07.

6. Allroggen H, Dennis G, Abbott RJ and Pye IF. New variant Creutzfeldt-Jakob disease: three case reports from Leicestershire. *Journal of Neurology, Neurosurgery and Psychiatry* 2000; 68: 375-378.

7. Henry C, Lowman A and Will RG. Creutzfeldt-Jakob disease in elderly people. *Age and Ageing* 2002; 31: 7-10.

8. Collinge J. Prion Diseases of Humans and Animals: Their Causes and Molecular Basis. *Annu. Rev. Neurosci.* 2001; 24: 519-50.

9. World Health Organisation. WHO Consultation on Public Health and Animal Transmissible Spongiform Encephalopathies: Epidemiology, Risk and Research Requirements. December 1999.

10. Wells GAH, Scott AD, Johnson CT et al. A novel progressive spongiform encephalopathy in cattle. *Vet. Rec.* 1987; 31: 419-20.

11. Bruce ME, Will RG, Ironside JW et al. Transmissions to mice indicate that "new variant" CJD is caused by the BSE agent. *Nature* 1997; 389: 498-501.

12. Collinge J, Sidle KCL, Meads J, Ironside J and Hill AF. Molecular analysis of prion strain variation and the aetiology of "new variant" CJD. *Nature* 1996; 383: 685-690.

13. Spielmeyer W. die histopathologische Forschung in der Psychiatrie. *Klin. Wochenschrift* 1922; 2: 1817-19.

14. Cuillé J, Chelle PL. La maladie dite tremblante du mouton est-elle inocuable? *C. R. Acad. Sci.* 1936; 230 : 1552-54.

15. Gajdusek DC, Gibbs CJ Jr, Alpers MP. Experimental transmission of kuru-like syndrome to chimpanzees. *Nature* 1966; 209: 794-96.

16. Gibbs CJ Jr, Gajdusek DC, Asher DM et al. Creutzfeldt-Jakob Disease (spongiform encephalopathy): transmission to the chimpanzee. *Science* 1968; 161: 388-89.

17. Masters CL, Gajdusek DC, Gibbs CJ Jr. Creutzfeldt-Jakob disease virus isolations from the Gerstmann-Straussler syndrome with an analysis of the various forms of amyloid plaque deposition in the virus induced spongiform encephalopathies. *Brain* 1981; 104: 559-88.

18. Alper T, Haig DA, Clarke MC. The exceptionally small size of the scrapie agent. *Biochem. Biophys. Res. Commun.* 1966; 22: 278-84.

19. Alper T, Cramp WA, Haig DA, Clarke MC. Does the agent of scrapie replicate without nucleic acid? *Nature* 1967; 214: 764-66.

20. Griffith JS. Self replication and scrapie. *Nature* 1967; 215: 1043-44.

21. Prusiner SB. Novel proteinaceous infectious particles cause scrapie. *Science* 1982 ; 216 : 136-44.

22. Pan K-M, Baldwin MA, Nguyen J et al. Conversion of α-helices into β-sheets features in the formation of the scrapie prion proteins. *Proc. Natl. Acad. Sci. USA* 1993; 90: 10962-66.

23. Meyer RK, McKinley MP, Bowman KA, Braunfeld MB, Barry RA, Prusiner SB. Separation and properties of cellular and scrapie prion proteins. *Proc. Natl. Acad. Sci. USA* 1986; 83: 2310-14.

24. Prusiner SB, Scott M, Foster D et al. Transgenetic studies implicate interactions between homologous PrP isoforms in scrapie prion replication. *Cell* 1990; 63: 673-686.

25. Brown P, Goldfarb LG, Gajdusek DC. The new biology of spongiform encephalopathy: infectious amyloidoses with a genetic twist. *Lancet* 1991; 337: 1019-22.

26. Hill AF, Desbruslais M, Joiner S et al. The same prion strain causes vCJD and BSE. *Nature* 1997; 389: 448-450.

27. Parchi P, Giese A, Capellari S et al. Classification of Sporadic Creutzfeldt-Jakob Disease Based on Molecular and Phenotypic Analysis of 300 Subjects. *Ann Neurol* 1999; 46: 224-233.

28. Collinge J, Palmer MS, Dryden AJ. Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease. *Lancet* 1991; 337: 1441-42.

29. Hsiao K, Baker HF, Crow TJ et al. Linkage of a prion protein missense variant to Gerstmann-Straussler syndrome. *Nature* 1989; 338: 342-45.

30. Collinge J, Owen F, Poulter M et al. Prion dementia without characteristic pathology. *Lancet* 1990; 336: 7-9.

31. Collinge J, Brown J, Hardy J et al. Inherited Prion Disease With 144 Base Pair Gene Insertion. 2. Clinical and Pathological Features. *Brain* 1992; 115: 687-710.

32. Duffy P, Wolf J, Collins G et al. Possible Person-To-Person Transmission Of Creutzfeldt-Jakob Disease. *New England Journal of Medicine* 1974; 290: 692-93.

33. Will RG, Matthews WB. Evidence for case-to-case transmission of Creutzfeldt-Jakob disease. *Journal of Neurology, Neurosurgery and Psychiatry* 1982; 45: 235-38.

34. Bernoulli C, Siegfried J, Baumgartner G. Danger of accidental person-to-person transmission of Creutzfeldt-Jakob disease by surgery. *Lancet* 1997; 1: 478-79 (letter).

35. Thadani V, Penar PL, Partington J et al. Creutzfeldt-Jakob disease probably acquired from a cadaveric dura mater graft. *Journal of Neurosurgery* 1988; 69: 766-69.

36. Powell-Jackson J, Kennedy P, Whitcombe EM et al. Creutzfeldt-Jakob disease and administration of human growth hormone. *Lancet* 1985; ii: 244-46.

37. Cochius JI, Burns RJ, Blumberg PC, Mack K, Alderman CP. Creutzfeldt-Jakob disease in a recipient of human pituitary-derived gonadotrophin. *Aust N Z J Med* 1990; 20(4): 592-93.

38. Brown P, Preece MA, Will RG. "Friendly fire" in medicine: hormones, homografts and Creutzfeldt-Jakob disease. *Lancet* 1992; 340: 24-27.

39. Brown P, Preece M, Brandel J-P et al. Iatrogenic Creutzfeldt-Jakob disease at the millennium. *Neurology* 2000; 55: 1075-81.

40. Will RG, Ironside JW, Zeidler M et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996; 347: 921-25.

41. Schiermeier Q. Testing times for BSE. *Nature* 2001; 409 (6821): 658-9.

42. Monreal J, Collins GH, Masters CL et al. Creutzfeldt-Jakob disease in an adolescent. *Journal of the Neurological Sciences* 1981; 52: 341-350.

43. Brown P, Cathala F, Labauge R, Pages M, Alary JC and Baron H. Epidemiologic Implications of Creutzfeldt-Jakob Disease In A 19 Year-Old Girl. *Eur J Epidemiol.* 1985; 1(1): 42-47.

44. Berman PH, Davidson GS and Becker LE. Progressive Neurological Deterioration in a 14-Year-Old Girl. *Pediatr Neurosci* 1988; 14: 42-49.

45. Kulczycki J, Jedrzejowska H, Gajkowski K, Tarnowska-Dziduszko E and Lojkowska W. Creutzfeldt-Jakob Disease in Young People. *European Journal Of Epidemiology* 1991; 7(5): 501-504.

46. Cousens SN, Zeidler M, Esmonde TF et al. Sporadic Creutzfeldt-Jakob disease in the United Kingdom: analysis of epidemiological surveillance data for 1970-96. *BMJ* 1997; 315: 389-95.

47. Will RG, Alperovitch A, Poser S et al. Descriptive Epidemiology of Creutzfeldt-Jakob Disease in Six European Countries, 1993-1995. *Ann Neurol* 1998; 43: 763-67.

48. Cousens S, Smith PG, Ward H et al. Geographical distribution of variant Creutzfeldt-Jakob disease in Great Britain, 1994-2000. *Lancet* 2001; 357: 1002-07.

49. Ashraf H. UK investigators put forward theory for vCJD cluster. *Lancet* 2001; 357: 937.

50. Colchester ACF and Brown PJ. Cluster of vCJD cases in Kent and its importance. *Lancet* 1999; 353: 1357.

51. Williams DJ. Cluster of vCJD cases in Kent and its importance. *Lancet* 1999; 353: 1357-1358.

52. Aylin P, Bunting J, De Stavola B, Coleman MP. Mortality from dementia in occupations at risk of exposure to bovine spongiform encephalopathy: analysis of death registrations. *BMJ* 1999; 318: 1044-5.

53. Ghani AC, Donnelly CA, Ferguson NM and Anderson RM. Assessment of the prevalence of vCJD through testing tonsils and appendices for abnormal prion protein. *Proc. R. Soc. Lond. B* 2000; 267: 23-29.

54. Bacchetti P. Unexamined assumptions in explorations of upper limit for cases of variant Creutzfeldt-Jakob disease. *Lancet* 2001; 357: 3-4.

55. Hilton DA, Fathers E, Edwards P et al. Prion immunoreactivity in the appendix before the clinical onset of new variant Creutzfeldt-Jakob disease. *Lancet* 1998; 352: 703-04.

56. Ironside JW, Hilton DA, Ghani A et al. Retrospective study of prion-protein accumulation in tonsil and appendix tissues. *Lancet* 2000; 355: 1693-94.

57. Hilton DA, Ghani AC, Conyers L et al. Accumulation of prion protein in tonsil and appendix: review of tissue samples. *BMJ* 2002; 325: 633-34.

58. Will RG, Cousens SN, Farrington CP, Smith PG, Knight RSG and Ironside JW. Deaths from variant Creutzfeldt-Jakob disease. *Lancet* 1999; 353: 979.

59. Andrews NJ, Farrington CP, Ward HJT et al. Deaths from variant Creutzfeldt-Jakob disease in the UK. *Lancet* 2003; 361:751-52.

60. Majeed A, Lehmann P, Kirby L, Knight R and Coleman M. Extent of misclassification of death from Creutzfeldt-Jakob disease in England 1979-96: retrospective examination of clinical records. *BMJ* 2000; 320: 145-7.

61. Hillier CEM, Salmon RL, Neal JW and Hilton DA. Possible underascertainment of variant Creutzfeldt-Jakob disease: a systematic study. *J Neurol Neurosurg Psychiatry* 2002; 72: 304-309.

62. Verity CM, Nicoll A, Will RG, Devereux G and Stellitano L. Variant Creutzfeldt-Jakob disease in UK children: a national surveillance study. *Lancet* 2000; 356: 1224-27.

63. Will RG, Zeidler M, Stewart GE et al. Diagnosis of New Variant Creutzfeldt-Jakob Disease. *Ann Neurol* 2000; 47: 575-582.

64. Silverdale M, Leach JP, Chadwick DW. New variant Creutzfeldt-Jakob disease presenting as localization-related epilepsy. *Neurology* 2000; 54: 2188.

65. Reuber M, Al-Din ASN, Baborie A, Chakrabarty A. New variant Creutzfeldt-Jakob disease presenting with loss of taste and smell. *J Neurol Neurosurg Psychiatry* 2001; 71: 412-18.

66. Seipelt M, Zerr I, Nau R et al. Hashimoto's encephalitis as a differential diagnosis of Creutzfeldt-Jakob disease. *J Neurol Neurosurg Psychiatry* 1999; 66: 172-76.

67. Zerr I, Pocchiari M, Collins S et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology* 2000; 55: 811-15.

68. Will RG, Zeidler M, Brown P, Harrington M, Lee KH, Kenney KL. Cerebrospinal-fluid test for new-variant Creutzfeldt-Jakob disease. *Lancet* 1996; 348: 955.

69. Frantz S. Heartbeat clue to diagnosing vCJD. *Nature Medicine* 2002; 8(5): 431.

70. Spencer MD, Knight RSG, Will RG. First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note review of early psychiatric and neurological features. *BMJ* 2002; 324: 1479-82.

71. Hill AF, Zeidler M, Ironside J, Collinge J. Diagnosis of new variant Creutzfeldt-Jakob disease by tonsil biopsy. *Lancet* 1997; 349(9045): 99-100.

72. Hill AF, Butterworth RJ, Joiner S et al. Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. *Lancet* 1999; 353(9148): 183-9.

73. Ironside JW and Bell JE. Florid plaques and new variant Creutzfeldt-Jakob disease. *Lancet* 1997; 350: 1475.

74. Lantos PL, Bhatia K, Doey LJ et al. Is the neuropathology of new variant CJD and Kuru similar? *[Letter] Lancet* 1997; 350(9072): 187-8.

75. Brown P, Cathala F, Sadowsky D, Gajdusek DC. Creutzfeldt-Jakob Disease in France: II. Clinical Characteristics of 124 Consecutive Verified Cases during the Decade 1968-1977. *Ann Neurol* 1979; 6: 430-37.

76. Will RG and Matthews WB. A retrospective study of Creutzfeldt-Jakob disease in England and Wales 1970-79 I: Clinical features. *Journal of Neurology, Neurosurgery and Psychiatry* 1984; 47: 134-140.

77. Allen NHP, Gordon S, Hope T, Burns A. Manchester and Oxford Universities Scale for Psychopathological Assessment of Dementia (MOUSEPAD). *British Journal of Psychiatry* 1996; 169: 82-3.

78. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. *Biological Psychiatry* 1988; 23: 271-84.

79. Snaith RP, Baugh SJ, Clayden AD et al. The Clinical Anxiety Scale: an instrument derived from the Hamilton Anxiety Scale. *Br J Psych* 1982; 141: 518-23.

80. Gilewski MJ, Zelinski EM. Memory Functioning Questionnaire (MFQ). *Psychopharmacology Bulletin* 1988; 24: 665-70.

81. Teunisse S, Mayke M and Van Creval H. Assessing the severity of dementia. *Archives of Neurology* 1991; 48: 274-77.

82. Mann AH, Jenkins R, Cutting JC and Cowen PJ. The development and use of a standardized assessment of abnormal personality. *Psychological Medicine* 1981; 11: 839-847.

83. Goldberg D, Benjamin S, Creed F. Psychiatry in Medical Practice. Routledge UK 1989; 22-44.

84. Cummings J. Organic delusions: phenomenology, anatomical correlations and review. *British Journal of Psychiatry* 1985; 146: 184-97.

85. Rubin E, Drevets W and Burke A. The nature of psychotic symptoms in senile dementia of the Alzheimer type. *Journal of Geriatric Psychiatry and Neurology* 1988; 1: 16-20.

86. Burns A. Psychiatric phenomena in Alzheimer's Disease I: Disorders of thought content. *British Journal of Psychiatry* 1990; 157: 72-76.

87. Burns A. Psychiatric phenomena in Alzheimer's Disease II: Disorders of perception. *British Journal of Psychiatry* 1990; 157: 76-81.

88. Burns A. Psychiatric phenomena in Alzheimer's Disease III: Disorders of mood. *British Journal of Psychiatry* 1990; 157: 81-86

89. Burns A. Psychiatric phenomena in Alzheimer's Disease IV: Disorders of behaviour. *British Journal of Psychiatry* 1990; 157: 86-94.

90. Keshavan MS, Lishman WA, Hughes JT. Psychiatric presentation of Creutzfeldt-Jakob Disease. A case report. *British Journal of Psychiatry* 1987; 151: 260-63.

91. Azorin JM, Donnet A, Dassa D, Gambarelli D. Creutzfeldt-Jakob disease misdiagnosed as depressive pseudodementia. *Comprehensive Psychiatry* 1993; 34(1): 42-4.

92. Stevens EM, Lament R. Psychiatric presentation of Jakob-Creutzfeldt-Jakob disease. *Journal of Clinical Psychiatry* 1979; 40(10): 445-46.

93. Lopez OL, Berthier ML, Bacher JT, Boller F. Creutzfeldt-Jakob disease with features of obsessive-compulsive disorder and anorexia nervosa: the role of cortical-subcortical systems. *Neuropsychiatry, neuropsychology and behavioural neurology* 1997; 10(2): 120-24.

94. Lacayo A. Mirthless Laughter in a Case of Creutzfeldt-Jakob Disease. *Journal of Neuropsychiatry* 1995; 7(3): 386-87.

95. Gallassi R, Morreale A, Montagna P et al. Fatal familial insomnia: Behavioral and cognitive features. *Neurology* 1996; 46: 935-939.

96. Scaravilli F, Cordery RJ, Kretzschmar H et al. Sporadic fatal insomnia: a case study. *Annals of Neurology* 2000; 48(4): 665-8.

97. Cordery RJ, Hall M, Cipolotti L et al. Early cognitive decline in Creutzfeldt-Jakob disease occurring in recipients of pituitary-derived human growth hormone. Abstract. *Association of British Neurologists Autumn Meeting* September 2001.

98. Alpers MP. Epidemiology and clinical aspects of Kuru, 1987. See Pruisner SB, McKinley MP eds. 1987. Prions: Novel Infectious Pathogens Causing Scrapie and Creutzfeldt-Jakob disease. San Diego: Academic.

99. Kapur N, Ironside J, Abbott P, Warner G and Turner A. A Neuropsychological-Neuropathological Case Study of Variant Creutzfeldt-Jakob Disease. *Neurocase* 2001; 7: 261-267.

100. Wechsler, D. Manual for the Wechsler adult intelligence scale revised. New York: Psychological Corporation, 1981.

101. Raven, J.C Coloured progressive Matrices. Oxford: Oxford Psychologists Press, 1976.

102. Warrington, E.K. Recognition memory tests. Windsor, UK: NFER-Nelson, 1984.

103. McKenna, P. & Warrington, E.K. The Graded Naming test. Windsor, UK: NFER-Nelson, 1984.

104. Oldfield, R.C. & Wingfield, A. Response latencies in naming objects. Quarterly Journal in Experimental Psychology, 1965, 18:273-281.

105. Nelson, H. The National Adult reading Test (NART): Test Manual. Windsor< UK: NFER-Nelson, 1982.

106. Warrington, E.K. & James. The visual object and space perception battery. Bury St Edmunds, UK: Thames Valley Test Company, 1991.

107. Nelson, H. A modified sorting test to frontal lobe deficits. Cortex, 1976, 12, 313-324.

108. Mcfie, J. & Piercy. Weigl Sorting Test. Journal of Mental Science, 1952, 98, 299-308.

109. Zeidler M, Sellar RJ, Collie DA et al. The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease. *Lancet* 2000; 355: 1412-18.

110. Steriade M, Jones EG, McCormick DA. The Primate Pulvinar: Structural, Functional and Behavioural Components of Visual Salience. In: Thalamus (Vol. II). Experimental and Clinical Aspects, 1997. Chapter 2, 53-91.

111. Westphal KP and Schachenmayr W. Computed tomography during Creutzfeldt-Jakob disease. *Neuroradiology*, 1985; 27: 362-364.

112. Kovanen J, Erkinjuntti T, Iivanaianen M, Ketonen L, Haltia M, Sulkava R, Sipponen JT. Cerebral MR and CT imaging in Creutzfeldt-Jakob Disease. *Journal of Computer Assisted Tomography,* 1985; Vol. 9, No. 1: 125-128.

113. Schlenska GK and Walter GF. Serial computed tomography findings in Creutzfeldt-Jakob disease. *Neuroradiology*, 1989; 31: 303-306.

114. Galvez S, Cartier L. Computed tomography findings in 15 cases of Creutzfeldt-Jakob disease with histological verification. *Journal of Neurology, Neurosurgery and Psychiatry* (1984); 47: 1244-1246.

115. Gertz H-J, Henkes H, Cervos-Navarro J. Creutzfeldt-Jakob disease: Correlation of MRI and neuropathologic findings. *Neurology*, 1988; 38: 1481-1482.

116. Milton WJ, Atlas SW, Lavi E, Mollman JE. Magnetic Resonance Imaging of Creutzfeldt-Jakob Disease. *Ann Neurol,* 1991; 29: 438-440.

117. DiRocco A, Molinari S, Stollman AL, Decker A, Yahr MD. MRI abnormalities in Creutzfeldt-Jakob disease. *Neuroradiology*, 1993; 35: 584-585.

118. Finkenstaedt M, Szudra A, Zerr I, Poser S, Hise J, Stoebner JM, Weber T. MR imaging of Creutzfeldt-Jakob Disease. *Radiology*, 1996; Vol. 199, No. 3: 793-798.

119. Samman I, Schulz-Schaeffer WJ, Wohrle JC, Sommer A, Kretzchmar HA, Hennerici M. Clinical range and MRI in Creutzfeldt-Jakob disease with heterozygosity at codon 129 and prion protein type 2. *J Neurol Neurosurg Psychiatry,* 1999; 67(5): 678-681.

120. Falcone S, Quencer RM, Bowen B, Bruce JH, Naldich TP. Creutzfeldt-Jakob Disease: Focal Symmetrical Cortical Involvement Demonstrated by MR imaging. *AJNR*, 1992; 13: 403-406.

121. Kruger H, Meesmann C, Rohrbach E, Muller J, Mertens HG. Panencephalopathic Type of Creutzfeldt-Jakob Disease with Primary Extensive Involvement of White Matter. *Eur Neurol*, 1990; 30: 115-119.

122. Uchino A, Yoshinaga M, Shiokawa O, Hata H, Ohno M. Serial MR imaging in Creutzfeldt-Jakob disease. *Neuroradiology*, 1991; 33: 364-367.

123. de Priester JA, Jansen GH, de Kruijk JR, Wilmink JT. New MRI findings in Creutzfeldt-Jakob disease: high signal in the globus pallidus on T1-weighted images. *Neuroradiology,* 1999; 41: 265-268.

124. Shyu W-C, Lee C-C, Hsu Y-D, Lin J-C, Lee J-T, Lee W-H, Tsao W-L. Panencephalitic Creutzfeldt-Jakob disease. Unusual presentation of magnetic resonance imaging and proton magnetic resonance spectroscopy. *Journal of the Neurological Sciences*, 1996; 138: 157-160.

125. Tzeng B-C, Chen C-Y, Lee C-C, Chen F-H, Chou T-Y, Zimmerman A. Rapid Spongiform Degeneration of the Cerebrum and Cerebellum in Creutzfeldt-Jakob Encephalitis: Serial MR findings. *AJNR*, 1997; 18: 583-586.

126. Rother J, Schwartz A, Harle M, Wentz KU, Berlit P, Hennerici M. Magnetic resonance imaging follow-up in Creutzfeldt-Jakob disease. *J Neurol*, 1992; 239: 404-406.

127. Ishida S, Sugino M, Koizumi N, Shinoda K, Ohsawa N, Ohta T, Kitamoto T, Tateishi J. Serial MRI in early Creutzfeldt-Jakob disease with a point mutation of prion protein at codon 180. *Neuroradiology*, 1995; 37: 531-534.

128. Schroter A, Zerr I, Henkel K, Tschampa HJ, Finkenstaedt M, Poser S. Magnetic Resonance Imaging in the Clinical Diagnosis of Creutzfeldt-Jakob Disease. *Archives of Neurology,* 2000; 57: 1751-1757.

129. Coulthard A, Hall K, English PT, Ince PG, Burn DJ, Bates D. Quantitative analysis of MRI signal intensity in new variant Creutzfeldt-Jakob Disease. *British Journal of Radiology* 1999; 72(860): 742-48.

130. Hojjat A, Collie D, Colchester A.C.F. The Putamen Intensity Gradient in CJD Diagnosis. *In: T. Dohi and R. Kikinis (Eds.): Medical Image Computing and Computer-Assisted Intervention* 2002, Berlin: Springer, pp524-532.

131. Colchester ACF, Hojjat SA, Will RG, Collie DA. Quantitative Validation Of MR Intensity Abnormalities In Variant CJD. *Journal of Neurology, Neurosurgery and Psychiatry* 2002; 73: 216 (Abstract).

132. Fox NC, Freeborough PA, Rossor MN. Visualisation and quantification of rates of atrophy in Alzheimer's disease. *Lancet*, 1996; 348 No. 9020: 94/97.

133. Fox NC, Freeborough PA, Mekkaoui KF, Stevens JS, Rossor MN. Cerebral and cerebellar atrophy on serial magnetic resonance imaging in an initially symptom free subject at risk of familial prion disease. *BMJ*, 1997; 315: 856-857.

134. Pantel J, Schroder J, Essig M, Jauss M, Schneider G, Eysenbach K, von Kummer R, Baudendistel K, Schad LR, Knopp MV. In vivo Quantification of Brain Volumes in Subcortical Vascular Dementia and Alzheimer's Disease. *Dement Geriatr Cogn Disord*, 1998; 9: 309-316.

135. Owen F, Poulter M, Lofthouse R, et al. Insertion in prion protein gene in familial Creutzfeldt-Jakob disease. *Lancet*, 1989; 1: 51-52.

136. Freeborough PA, Fox NC, Kitney RI. Interactive algorithms for the segmentation and quantification of 3-D MRI brain scans. *Computer Methods and Programs in Biomedicine,* 1997; 53: 15-25.

137. Jackson GD and Duncan JS. MRI Neuroanatomy. 1996; Churchill Livingstone, USA.

138. Whitwell JL, Crum WR, Fox NC, Watt HC. Intracranial volume normalisation: Implications for longitudinal quantitative MRI. *American Journal of Neuroradiology,* in press.

139. Freeborough PA, Woods RP, Fox NC. Accurate Registration of Serial 3D MR Brain Images and Its Application to Visualizing Change in Neurodegenerative Disorders. *Journal of Computer Assisted Tomography,* 1996; 20(6): 1012-1022.

140. Fox NC, Freeborough PA. Brain Atrophy Progression Measured from Registered Serial MRI: Validation and Application to Alzheimer's Disease. *JMRI,* 1997; 7: 1069-1075.

141. Bland JM and Altman DG. Statistical Methods For Assessing Agreement Between Two Methods Of Clinical Measurement. *Lancet,* 1986; 1(8476): 307-310.

142. Jack CR, Peterson RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Tangalos EG, Kokmen E. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology,* 1998; 51: 993-999.

143. Fox NC, Scahill RI, Crum WR, Rossor MN. Correlation Between Rates Of Brain Atrophy And Cognitive Decline In Alzheimer's Disease. *Neurology,* 1999; 52: 1687-1689.

144. Bruhn H, Weber T, Thorwirth V, Frahm J. In-vivo monitoring of neuronal loss in Creutzfeldt-Jakob disease by proton magnetic resonance spectroscopy. *Lancet* 1991; 337: 1610-1611.

145. Graham GD, Petroff OAC, Blamire AM, Rajkowska G, Goldman-Rakic P, Prichard JW. Proton magnetic resonance spectroscopy in Creutzfeldt-Jakob disease. *Neurology* 1993; 43: 2065-2068.

146. Konaka K, Kaido M, Okuda Y et al. Proton magnetic resonance spectroscopy of a patient with Gerstmann-Straussler-Scheinker disease. *Neuroradiology* 2000; 42: 662-665.

147. Pandya HG, Coley SC, Wilkinson ID, Griffiths PD. Magnetic resonance spectroscopic abnormalities in sporadic and variant Creutzfeldt-Jakob disease *Clin Rad* 2003; 58: 148-153.

148. Provencher SW. Estimation of metabolic concentrations from localized in vivo proton NMR spectra. *Magn. Reson. Med.* 1993; 30(6): 672-9.

149. Valenzuela MJ, Sachdev P. Magnetic resonance spectroscopy in AD. *Neurology* 2001; 56: 592-598.

150. Salibi N and Brown MA. Clinical MR Spectroscopy. First Principles. Chapter 6; 143-202. Wiley-Liss, John Wiley & Sons, Inc. USA.

151. Huang W, Alexander GE, Daly EM et al. High brain myoinsitol levels in the predementia phase of Alzheimer's disease in adults with Down's syndrome. *Am. J. Psychiatry* 1996; 156: 1879-86.

152. Royal College of Psychiatrists, London 2000. Services for younger people with Alzheimer's disease and other dementias. *Council Report CR77.*

153. Newens A, Forster D, Kay D. Referral patterns and diagnosis in presenile Alzheimer's disease: implications for general practice. *British Journal of General Practice* 1994; 44: 404-407.

154. Baldwin R. Acquired cognitive impairment in the presenium. *Psychiatric Bulletin* 1994; 18: 463-465.

155. Allen H, Baldwin B. The referral, investigation and diagnosis of presenile dementia: two services compared. *International Journal of General Psychiatry* 1995; 10: 185-190.

156. Ferran J, Wilson K, Doran M, et al. The early onset dementias: A study of clinical characteristics and service use. *International Journal of Geriatric Psychiatry* 1996; 11: 863-869.

157. Waldemar G, Dubois B, Emre M, et al. Diagnosis and management of Alzheimer's disease and other disorders associated with dementia. The role of neurologists in Europe. *European Journal of Neurology* 2000; 7: 133-144.

158. American Academy of Neurology Quality Standards Subcommittee. Practice parameter for diagnosis and evaluation of dementia. *Neurology* 1994; 44: 2203-2206.

159. Royal College of Psychiatrists, London 1995. Consensus statement on the assessment and investigation of an elderly person with suspected cognitive impairment by a specialist old age psychiatry service. *Council Report CR 49.*

160. Royal College of Psychiatrists, London 2001. "Forgetful but not forgotten – assessment by a specialist service". Diagnostic Assessment and Investigation of Suspected Dementia by a Specialist Old Age Psychiatry Service. *Consensus Statement, 2000/2001.*

161. Branton T. Use of computerised tomography by old age psychiatrists: an examination of criteria for investigation of cognitive impairment. *International Journal of Geriatric Psychiatry* 1999; 14: 567-571.

162. Vickrey BG, Gifford DR, Belin TR, et al. Practice styles of US compared to UK neurologists. *Neurology* 1998; 50: 1661-1668.

163. Department Of Health, UK. National Service Framework for Older People, March 2001.

164. Douglas M, Campbell H, Will RG. Patients with new variant Creutzfeldt-Jakob Disease and their families: Care and information needs. *CJD Surveillance Unit, Edinburgh, UK,* February 1999.

APPENDICES

I DIAGNOSTIC CRITERIA FOR VARIANT CJD

I A) PROGRESSIVE NEUROPSYCHIATRIC DISORDER
B) DURATION OF ILLNESS > 6 MONTHS
C) ROUTINE INVESTIGATIONS DO NOT SUGGEST AN ALTERNATIVE DIAGNOSIS
D) NO HISTORY OF POTENTIAL IATROGENIC EXPOSURE

II A) EARLY PSYCHIATRIC SYMPTOMS *
B) PERSISTENT PAINFUL SENSORY SYMPTOMS **
C) ATAXIA
D) MYOCLONUS OR CHOREA OR DYSTONIA
E) DEMENTIA

III A) EEG DOES NOT SHOW THE TYPICAL APPEARANCE OF SPORADIC CJD ***(OR NO EEG PERFORMED)
B) BILATERAL PULVINAR HIGH SIGNAL ON MRI SCAN

IV A) POSITIVE TONSIL BIOPSY

DEFINITE: IA (PROGRESSIVE NEUROPSYCHIATRIC DISORDER) and NEUROPATHOLOGICAL CONFIRMATION OF vCJD ****

PROBABLE: I and 4/5 OF II and III A and III B
or I and IV A

*Depression, anxiety, apathy, withdrawal, delusions.

**This includes both frank pain and/ or unpleasant dysaesthesia

***Generalised triphasic periodic complexes at approximately one per second

****Spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum.

Issued by the Department of Health, February 2003.

II QUESTIONNAIRE

Survey to assess current practices in the diagnosis and management of young patients with dementia (i.e. patients with onset <65 years)

1. Please state **a)** your speciality and **b)** your grade

(tick as appropriate)

a) Neurologist ☐

Old Age Psychiatrist ☐

General Adult Psychiatrist ☐

General Physician ☐

Other (*please specify)* _____

b) Consultant/ Senior Lecturer ☐

Specialist Registrar/ Senior Registrar ☐

Clinical Assistant/ Associate Specialist ☐

Other (*please specify)* _____

2. Is there a specialist referral centre for the management of patients with young onset dementia,

a) in your trust? Yes ☐ No ☐

b) in your region? Yes ☐ No ☐

If No, go on to Q4

3. Are you part of the specialist team working in such a centre?

Yes ☐ No ☐

4. How many new patients with young onset dementia do you estimate that you see per year?

0 - 5 ☐ 5 - 10 ☐ 10 - 50 ☐ >50 ☐

5. Who do your referrals come from?

(tick as many as necessary)

General Practitioners ☐

Neurologists ☐

General Adult Psychiatrists ☐

Old Age Psychiatrists ☐

Social Services ☐

Other *(please specify)* _____

6. Do you refer patients with young onset dementia to any other specialists?

(choose more than one if appropriate)

	Approx. number of referrals per year
Regional dementia clinic	_____
Neurologist	_____
Old Age Psychiatrist	_____
General Adult Psychiatrist	_____
Clinical Geneticist	_____
Other *(please specify)* _____	

7. Would you refer on to a specialist or a specialist centre for patients with young onset dementia, if one were available?

Yes ☐ No ☐

8. Is there a specialist nurse in your unit to provide support and information to patients and carers?

Yes ☐ No ☐

9. Are the following points covered in history taking?

	Always	Often	Sometimes	Never
Independent history from carer	☐	☐	☐	☐
Detailed family history	☐	☐	☐	☐
Changes in personality *(such as eating habits, sexual behaviour)*	☐	☐	☐	☐
Symptoms of depression	☐	☐	☐	☐
Somatic symptoms	☐	☐	☐	☐
Driving history	☐	☐	☐	☐

10. **a)** Are the following covered on physical examination?

	Always	Often	Sometimes	Never
General physical examination	☐	☐	☐	☐
General neurological examination	☐	☐	☐	☐
b) Do you specifically look for?				
fasciculation	☐	☐	☐	☐
primitive reflexes	☐	☐	☐	☐
visual disorientation	☐	☐	☐	☐
extrapyramidal features	☐	☐	☐	☐

11. Which of the following investigations do you perform on your young patients with cognitive impairment?

	Always	Often	Sometimes	Never
Full blood count	☐	☐	☐	☐
Renal profile	☐	☐	☐	☐
Liver profile	☐	☐	☐	☐
Thyroid function	☐	☐	☐	☐
B12 and folate	☐	☐	☐	☐
ESR	☐	☐	☐	☐
Autoantibody screen	☐	☐	☐	☐
Antithyroid microsomal	☐	☐	☐	☐
Anticardiolipin Abs	☐	☐	☐	☐
Treponemal Serology	☐	☐	☐	☐

	Always	Often	Sometimes	Never
HIV	☐	☐	☐	☐
White cell enzymes	☐	☐	☐	☐
Plasma very long chain fatty acids	☐	☐	☐	☐
Heavy metal screening	☐	☐	☐	☐
Blood for genetic screening:				
Huntington's	☐	☐	☐	☐
DRPLA	☐	☐	☐	☐
Prion protein	☐	☐	☐	☐
APP, presenilin I,				
presenilin 2	☐	☐	☐	☐
tau gene	☐	☐	☐	☐
CT brain scan	☐	☐	☐	☐
MRI brain scan	☐	☐	☐	☐
MMSE	☐	☐	☐	☐
Neuropsychology	☐	☐	☐	☐
PET, SPECT	☐	☐	☐	☐
EEG	☐	☐	☐	☐
CSF	☐	☐	☐	☐
CSF (S100, NSE, P 14-3-3)	☐	☐	☐	☐
Tonsil biopsy	☐	☐	☐	☐
Brain biopsy	☐	☐	☐	☐

12. Are carers given the opportunity to speak to the doctor in the absence of the patient?

Always	Often	Sometimes	Never
☐	☐	☐	☐

Please state reasons

_____

_____

13. Do you pass on the diagnosis to patients with young onset dementia and their carers?

Always	Often	Sometimes	Never
☐	☐	☐	☐

14. Do you give the diagnosis to patients and their carers separately?

Always	Often	Sometimes	Never
☐	☐	☐	☐

Please state reasons

_____

_____

15. Are any other people present when the diagnosis is given e.g. Nurse Counsellor?

Yes ☐ *please say who*_____

No ☐

16. After you have made the diagnosis, on average how often will you see the patient with young onset dementia again?

Never ☐

Only if needed ☐

Annually ☐

Biannually ☐

Three monthly ☐

Monthly ☐

More often, *please specify* _____

17. Who is mainly responsible for follow up of the patient and their family? *(tick more than one if appropriate)*

General Practitioner ☐

Specialist dementia/ memory clinic ☐

Old Age Psychiatrist ☐

Consultant Neurologist ☐

Shared care ☐

Please specify _____

Other ☐

Please specify _____

18. Do you organise or give advice on the following?

	Always	Often	Sometimes	Never
referral to a CPN	☐	☐	☐	☐
contacting the DVLA	☐	☐	☐	☐
enduring power attorney	☐	☐	☐	☐
information on support groups *(such as Alzheimer's Disease Society, Pick's Disease Support Group,CJD support network)*	☐	☐	☐	☐
genetic counselling	☐	☐	☐	☐

19. Do you discuss any of the following?

	Always	Often	Sometimes	Never
Drug treatments	☐	☐	☐	☐
Entry into drug trials	☐	☐	☐	☐
Post mortem consent	☐	☐	☐	☐

20. Are you able to prescribe acetylcholinesterase inhibitors for young onset dementia patients?

Able to prescribe freely ☐

Prescribe under certain guidelines ☐

Very rarely able to prescribe ☐

Not at all ☐

Give private prescriptions ☐

21. Do you undertake the follow up of patients on acetylcholinesterase inhibitors?

Yes ☐ No ☐

Thank you

for taking the time to complete this questionnaire.

PUBLICATIONS RELATING TO THIS THESIS

Cordery RJ, Harvey R, Frost C, Rossor MN. National survey to assess current practices in the diagnosis and management of young people with dementia. *Int J Geriatr Psychiatry.* 2002 Feb; 17(2): 124-7.

Cordery RJ, Hall M, Cipolotti L, Al-Sarraj S, O'Donovan DG, Davidson L, Adlard P, Rossor MN. Early cognitive decline in Creutzfeldt-Jakob disease occurring in recipients of pituitary-derived human growth hormone. *Journal of Neurology, Neurosurgery and Psychiatry* 2003; 74(10): 1412-6..

Cordery RJ, Janssen JC, Fox NC, Whitwell JL, Crum WR, Collinge J, Rossor MN. Cross-sectional Volumetric MRI Measurement of Whole Brain and Cerebellum Distinguishes Patients with Creutzfeldt-Jakob disease from Normal Controls. *Abstract. (WCN 2001) Journal of the Neurological Sciences, Vol. 187, Supplement 1, June 15, 2001, S221-222.*

Cordery RJ, Hall M, Cipolotti L, Al-Sarraj S, O'Donovan DG, Davidson L, Adlard P, Rossor MN. Early cognitive decline in human growth hormone associated Creutzfeldt-Jakob disease. *Abstract. Association of British Neurologists Autumn meeting 2001.*

Scaravilli F. **Cordery** RJ. Kretzschmar H. Gambetti P. Brink B. Fritz V. Temlett J. Kaplan C. Fish D. An SF. Schulz-Schaeffer WJ. Rossor MN. Sporadic fatal insomnia: a case study. *Annals of Neurology,* 48(4): 665-8, 2000 Oct.

Manuscripts submitted or in preparation

Cordery RJ, Alner K, Cipolotti L, Kennedy A, Ron M, Collinge J, Rossor MN. The neuropsychology of variant CJD: A comparative study of cases with familial and sporadic forms of prion disease. *Submitted to Journal of Neurology, Neurosurgery and Psychiatry.*

Cordery RJ, Rossor MN, MacManus D, Collinge J, Waldman AD. Proton magnetic spectroscopy in variant Creutzfeldt-Jakob disease. Abstract *accepted for the ISMRM 2003.*

Cordery RJ, Janssen JC, Fox NC, Whitwell JL, Price S, Crum WR, Collinge J, Rossor MN. Cross-sectional Volumetric MRI Measurement of Whole Brain and Cerebellum Distinguishes Patients with Creutzfeldt-Jakob Disease from Normal Controls. *In preparation.*

Cordery RJ, RossorMN, MacManus D, Godbolt A, Collinge J, Waldman AD. Proton magnetic spectroscopy in variant Creutzfeldt-Jakob disease. *In preparation.*

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